PART I

TOTAL SYNTHESIS AND BIOLOGICAL EVALUATION OF ANTILLATOXIN AND FRAGMENTS

PART II

SYNTHETIC STUDIES TOWARDS THE TOTAL SYNTHESIS OF CYTOCHALASANS AND TUBEROSTEMONINE

APPENDIX

SILICON-ASSISTED PROPARGYLIC TRANSFER TO ALDEHYDES

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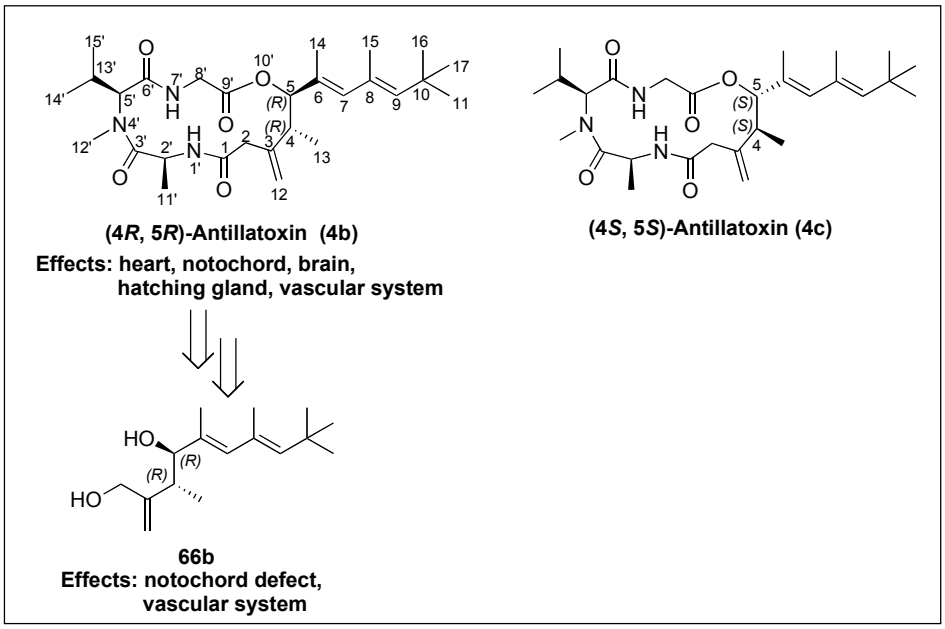
SUMMARY

Part I

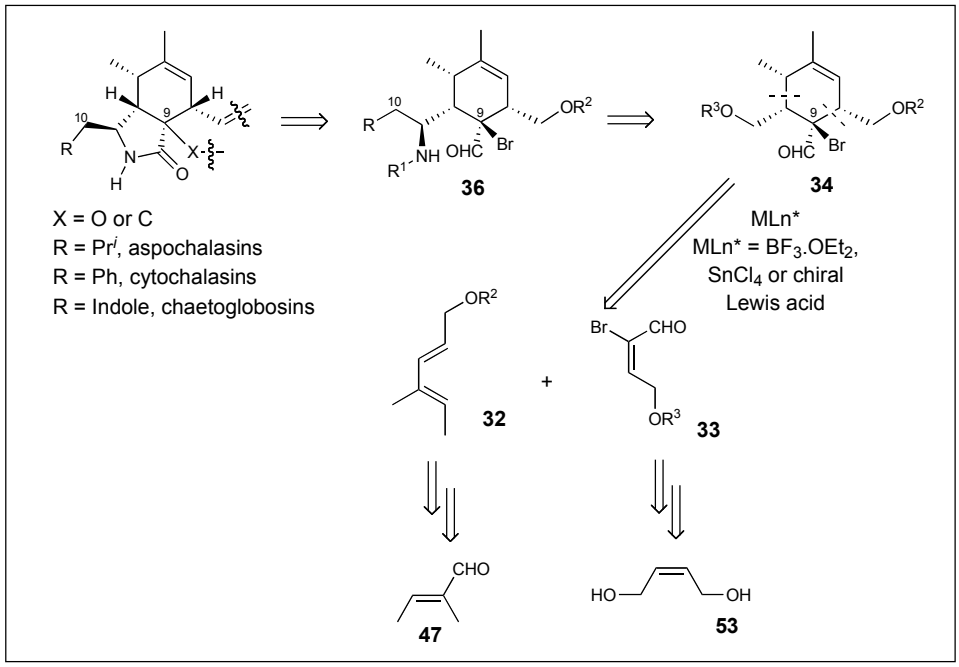
The total synthesis of natural (4*R*, 5*R*)-antillatoxin **4b** and its analogue (4*S*, 5*S*)-antillatoxin **4c** has been achieved in 9 steps (from bromide **43** and aldehyde **41** - strategy 2) in 23% overall yield. Our strategy provides practical and easy entry into key intermediates and analogues. Notable features of this synthesis include the indium-mediated allylation of a secondary allylic bromide with aldehyde in aqueous media, and an oxidation-reduction sequence to control the two chiral centres at C_4 and C_5. Especially noteworthy is the convergent nature of this synthetic strategy and the incorporation of all the necessary functionalities in the early stages of the synthesis. The procedure developed here can be used for large scale synthesis of other biologically interesting natural products.



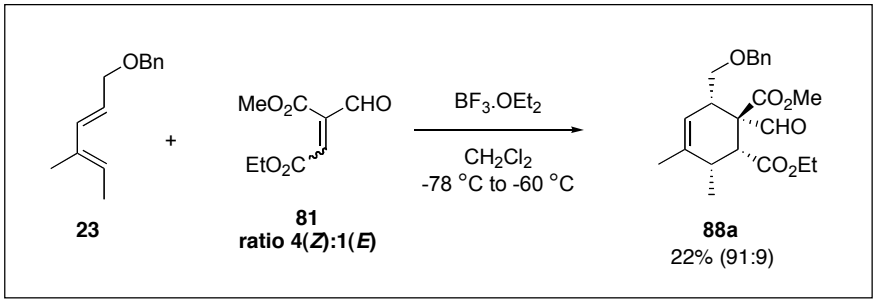
Screening of this library of simpler fragments obtained during the process of the total synthesis compounds has resulted in the discovery of other potent compounds. This simple screen utilizing zebrafish embryos has resulted in the discovery of bioactive fragments (4*R*, 5*R*)-**66b** which display similar behavior as (4*R*, 5*R*)-antillatoxin. These interesting results provide further evidence on the ease and usefulness of zebrafish embryos as a simple tool for fast biological evaluation in drug discovery research.

Part II

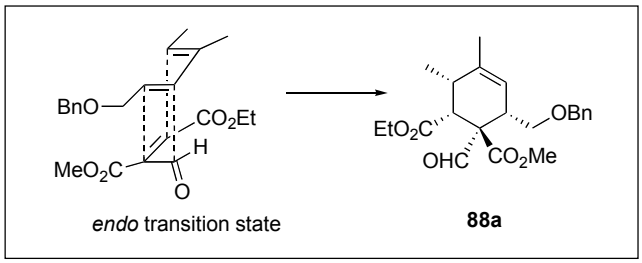
In Chapter 2, synthetic studies towards the total synthesis of cytochalasans is reported. Retrosynthetic analysis of cytochalasans gives the key intermediate **36** with a bromine substituent at the C-9 position. Key intermediate **36** was envisaged to be constructed from a Lewis acid catalyzed intermolecular Diels-Alder reaction of diene **32** and dienophile **33**.



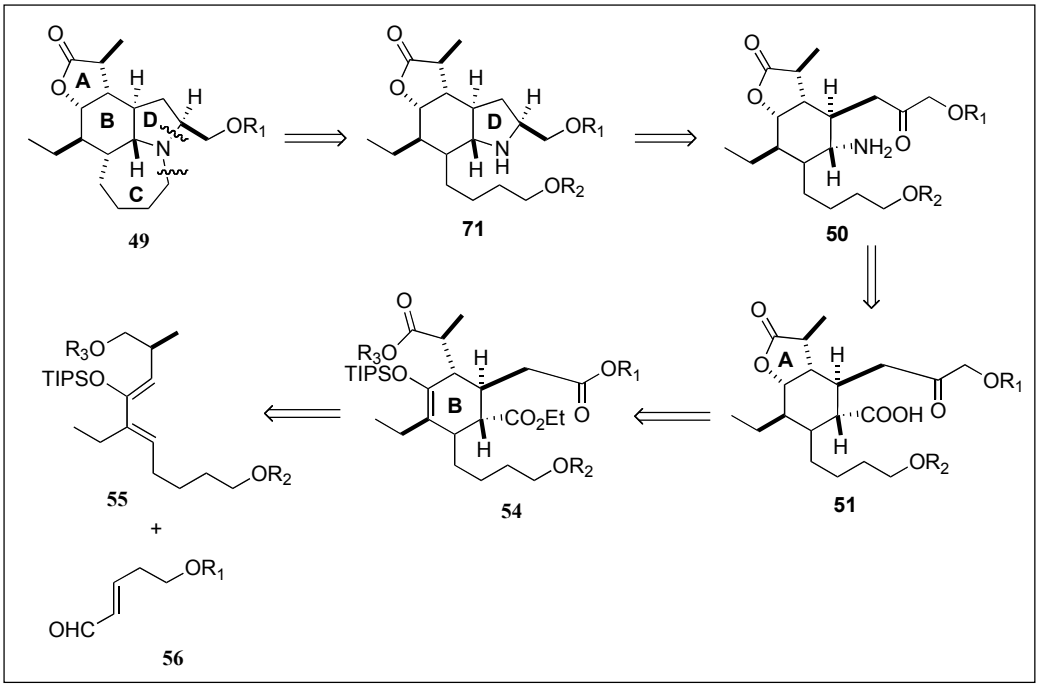
We managed to build the desired six-membered cyclohexane ring system in the key fragment **36** with the correct stereochemistry, which is the core ring skeleton found in the cytochalasans class of natural products. By treating the crude aldehyde **81** and diene **23** with $BF_3.OEt_2$ in dichoromethane, we obtained cycloadduct **88a** as a colorless oil in 22% yield after 16 hours of reaction at -60 °C. In the reaction, we found that only the minor (*E*)-isomer went through the normal [4+2] Diels-Alder cycloaddition reaction.



The regiochemistry and relative stereochemistry of the cycloadducts **88a** were elucidated by ^{1}H NMR, ^{13}C (DEPT), COSY, NOESY, HMQC and HMBC as depicted in Figure 2-10. The stereochemistry of the products suggests that due to the secondary orbital interaction, the Diels-Alder reaction had proceeded *via* an *endo* transition state giving product **88a**.

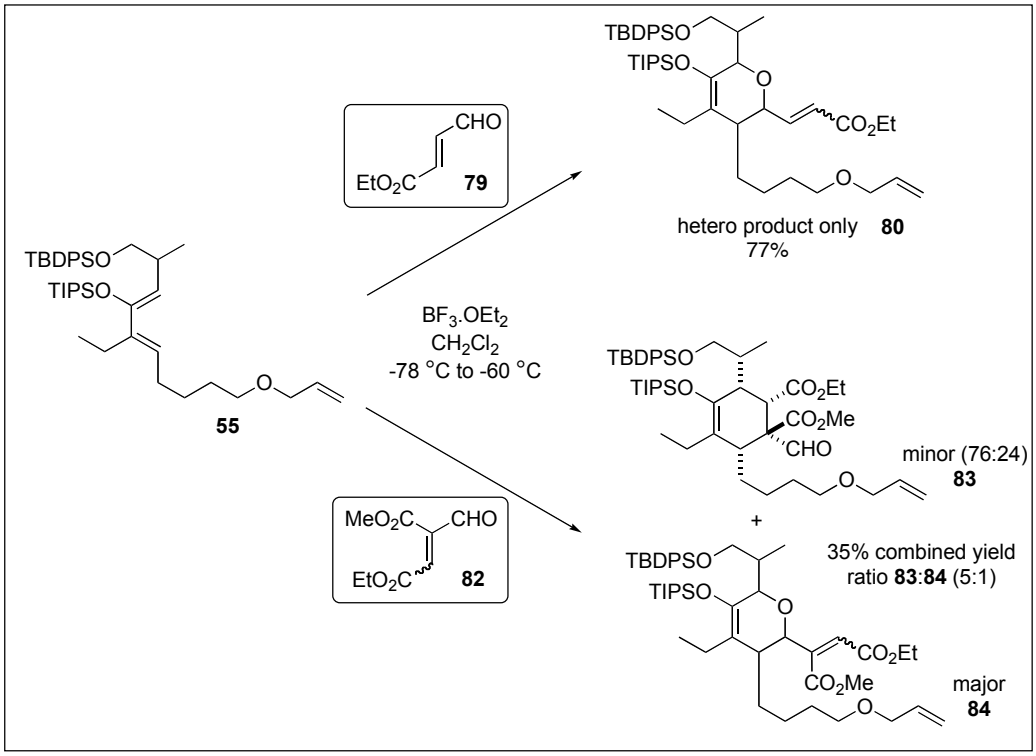


In Chapter 3, the synthetic studies towards the total synthesis of tuberostemonine is reported. Our key step relies on the intermolecular Diels-Alder reaction between diene **55** and dienophile **56** to construct ring B. An amino group would be introduced to the ring system through Curtius rearrangement and followed by reductive amination to construct the pyrrolidine ring D. Finally, closure of the seven-membered ring C was achieved by the conversion of the protecting group followed by a S_N2 reaction on the amino group.



The core ring B was planned to be achieved from diene **55** and dienophile **56**. However, no desired products were obtained. Further investigation with aldehyde-ester **79** as dienophile, only the hetero-Diels-Alder product **80** was obtained from the reaction mixture. Exploration with dienophile **82** afforded the mixture of normal Diels-Alder cycloadduct **83** and hetero-Diels-Alder product **84**. Even though cycloadduct **83** is not the desired product for the total synthesis of tuberostemonine,

this finding will still be useful in other synthesis which require more complicated diene such as diene **55**.



INDEX OF ABBREVIATIONS

δ	chemical shift
(((	sonication
Δ	reflux
ºC	degree centrigrade
Ac	acetyl
AcOH	acetic acid
AIBN	*azo-bis*-isobutyronitrile
Alloc	allyloxycarbonyl
Ala	alanine
aq.	aqueous
9-BBN	9-borabicyclo[3.3.1]nonane
Bn	benzyl
BOC	tert-butoxycarbonyl
BOP	benzotriazol-1-yloxytris (dimethylamino) phosphonium hexafluorophosphate
brs	broad singlet
Bz	benzoyl
t-bu	tert-butyl
cacld	calculated
cat	catalytic
Cbz	benzyloxycarbonyl
$CDCl_3$	deuterated chloroform
COSY	correlated spectroscopy
Cp	cyclopentadienyl
CSA	camphorsulfonic acid
CH_2Cl_2	dichoromethane
$CHCl_3$	chloroform
cm^{-1}	inverse centimeter
cyc	cyclohexane; cyclohexenyl
d	doublet
DABCO	1,4-diazabicyclo[2.2.2]octane

dba	dibenzylidene acetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	1,3-dicyclohexylcarbodiimide
dd	doublets of doublet
de	diastereomeric excess
DIBAL	diisobutylaluminium hydride
DIEA	diisopropylethylamine
DMAP	4-(*N,N*-dimethylamino)pyridine
DMF	dimethylformamide
DMP	Dess-Martin periodinane
DMSO	dimethyl sulfoxide
DPPA	diphenylphosphoryl azide
dt	doublets of triplet
dq	doublets of quartet
EDC	1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride
ee	enantiomeric excess
EI	electron impact ionization
equiv.	equivalent
ESI	electronspray ionization
Et	ethyl
ether	diethyl ether
Et_3N	triethylamine
EtOAc	ethyl aceate
EtOH	ethanol
FAB	fast atomic bombardment
Fmoc	9-fluorenylmethyl
FTIR	Fourier transform infrared spectroscopy
Gly	glycine
g	gram
h	hour
H	hydrogen
Hex	hexane
HMBC	heteronuclear multiple bond correlation
HMPA	hexamethylphosphoramide

HMQC	heteronuclear multiple quantum correlation
HOBt	1-hydroxybenzotriazole
HRMS	high resolution mass spectroscopy
Hz	Hertz
IR	infrared
i-Pr	isopropyl
J	coupling constants
kg	kilogram
LDA	lithium diisopropylamide
LiHMDS	Lithium hexamethyl disilazide
M	concentration (mol/dm^{-3})
M^+	parent ion peak (mass spectrum)
m	multiplet
m-CPBA	*meta*-chloroperoxybenzoic acid
Me	methyl
MEM	2-methoxyethoxy methyl
MeOH	methanol
mg	milligram
MHz	Megahertz
min	minute
mmol	millimoles
mol	moles
MPM	*p*-methoxyphenyl methyl
MS	mass spectrum
Ms	methanesulfonyl
N	concentration (normality)
NBS	*N*-bromosuccinimide
n-Bu	*n*-butyl
NMR	nuclear magnetic resonance
NOE	nuclear overhauser effect
NOESY	nuclear overhauser enhancement spectroscopy
obsd.	observed
OTf	trifluoromethanesulfonate
p	page

PBr_3	phophorus tribromide
PCC	pyridinium chlorochromate
Pd	palladium
$Pd(PPh_3)_4$	tetrakis(triphenylphosphine)palladium(0)
Ph	phenyl
ppm	parts per million
Py	pyridine
PyBrOP	bromotripyrrolidinophosphonium hexafluorophosphate
q	quartet
rt.	room temperature
RBF	round bottom flask
R_f	retention factor
s	singlet
sat.	saturated
t	triplet
TBAF	tetrabutylammonium fluoride
TBDMS	*tert*-butyldimethyl silyl
TBDPS	*tert*-butyldiphenyl silyl
t-BOC	*tert*-butoxycarbonyl
t-Bu	*tert*-butyl
td	triplets of doublet
TFA	trifluoroacetic acid
THF	tetrahydrofuran
THP	tetrahydropyran
TIPS	triisopropyl silyl
TLC	thin layer chromatography
TMSCl	trimethylsilyl chloride
TPAP	tetrapropylammonium perruthenate
Troc	2,2,2-trichloroethoxycarbonyl
Ts	*p*-toluenesulfonyl
Val	valine
vol	volume

PART I

Chapter 1

Total Synthesis and Biological Evaluation of Antillatoxin and Fragments

1.1 Historical Background

Marine cyanobacteriums are well known to be the rich source of structurally unique neurotoxic secondary metabolites (eg. Brevetoxin B[1] (**1**), Curacin A[2] (**2**), Barbamide[3] (**3**), Antillatoxin[4] (**4b**) etc as shown in Figure 1-1. Antillatoxin (**4b**) is one of this marine toxins, isolated from the pantropical marine cyanobacterium *Lyngbya majuscula*. It is a structurally novel lipopeptide with high degree of methylation and without close parallel to any other known marine natural product. To date, it is one of the most ichthyotoxic compounds isolated from marine sources. Its toxicity measurements with goldfish recorded a $LD_{50} = 0.05$ μg/mL, and it is only exceeded in potency by brevetoxins ($LD_{50} = 0.003$ μg/mL).[4,5]

More recently, it has been shown to be neurotoxic in primary cultures of rat cerebellar granule cells. In the latter study, morphological evidences of antillatoxin-induced neurotoxicities included swelling of neuronal somata, thinning of neurites, and blebbing of neurite membranes. Lactate dehydrogenase efflux monitoring demonstrates that antillatoxin also induced a concentration-dependent cytotoxicity in

[1] Lin, Y. -Y; Risk, M.; Ray, S. M.; Engen, D. V.; Clardy, J.; Golik, J.; James, J. C.; Nakanish, K. *J. Am. Chem. Soc.* **1981**, *103*, 6773-6775.

[2] Gerwick, W. H.; Proteau, P. J.; Nagle, D. G.; Hamel, E.; Blokhin, A.; Slate, D. L. *J. Org. Chem.* **1994**, *59*, 1243.

[3] Orjala, J.; Gerwick, W. H. *J. Nat. Prod.* **1996**, *59*, 427.

[4] Orjala, J.; Nagle, D. G.; Hsu, V. L.; Gerwick, W. H. *J. Am. Chem. Soc.* **1995**, *117*, 8281-8282.

[5] (a) Berman, F. W.; Gerwick, W. H.; Murray, T. F. *Toxicon* **1999**, *37*, 1645-1648. (b) Wu, M.; Okino, T.; Nogle, L. M.; Marquez, B. L.; Williamson, R. T.; Sitachitta, N.; Berman, F. W.; Murray, T. F.; McGough, K.; Jacobs, R. *et al. J. Am. Chem. Soc.* **2000**, *122*, 12041-12042. (c) Lin, Y. -Y.; Risk, M.; Ray, S. M.; Engen, D.V.; Clardy, J.; Golik, J.; James, J. C.; Nakanishi, K. *J. Am. Chem. Soc.* **1981**,*103*, 6773.

cerebellar granule neurons. This neurotoxic response of antillatoxin was prevented by either *N*-methyl-D-aspartate (NMDA) receptor antagonists or tetrodotoxin.[5,6]

At the outset of this investigation, we were aware that only small amount of antillatoxin had been isolated (1.3 mg, 0.07% of extract).[4] The successful outcome of synthetic antillatoxin would aid in the production of enough quantities for detailed biological evaluations.

The isolation of antillatoxin (**4b**) was reported by Gerwick and co-workers in 1995. Based on spectroscopic studies (1D and 2D NMR) and molecular modeling using a dynamic simulated annealing protocol with the program XPLOR, they deduced that the structure of antillatoxin as 4*S*, 5*R* configuration at C_4 and C_5.[4] However, the structure was later revised to be 4*R*, 5*R* configuration by T. Shiori[7] and J. Whites[8] groups.

[6] (a) Li, W. I.; Berman, F. W.; Okino, T.; Yokokawa, F.; Shioiri, T.; Gerwick, W. H.; Murray, T. F. *Proc. Natl. Acad. Sci. U.S.A.* **2001**, *98*, 7599-7604. (b) Li, W. I., Marquez, B. L., Okino, T., Yokokawa, F., Shioiri, T., Gerwick, W. H., Murray, T. F. *J. Nat. Prod.* **2004**, *67*, 559-568.

[7] (a) Yokokawa, F.; Shioiri. T. *J. Org. Chem.* **1998**, *63*, 8638-8639; (b) Yokokawa, F.; Fujiwara, H.; Shioiri. T. *Tetrahedron Lett.* **1999**, *40*, 1915-1916. (c) Yokokawa, F.; Fujiwara, H.; Shioiri. T. *Tetrahedron* **2000**, *56*, 1759-1775.

[8] White, J. D.; Hanselmann, R.; Wardrop, D. *J. Am. Chem. Soc.* **1999**, *121*, 1106-1107.

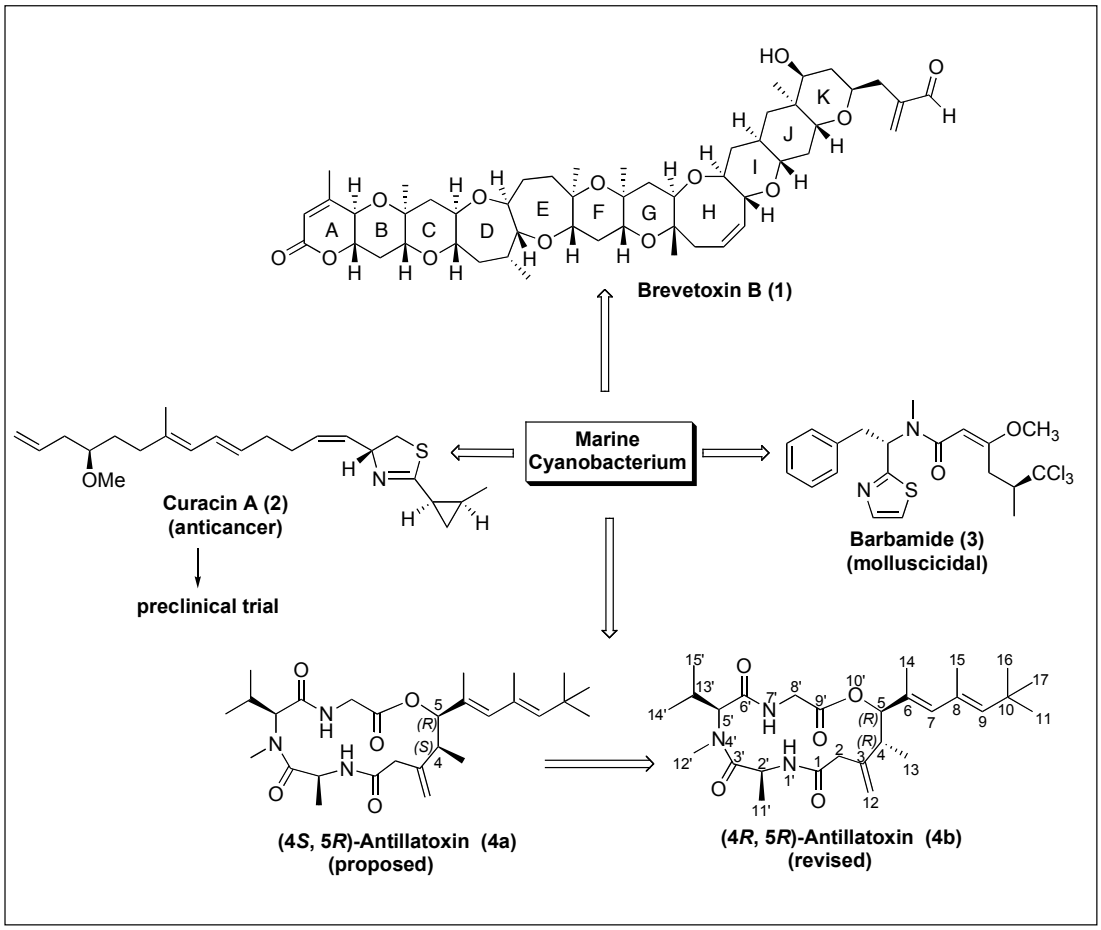


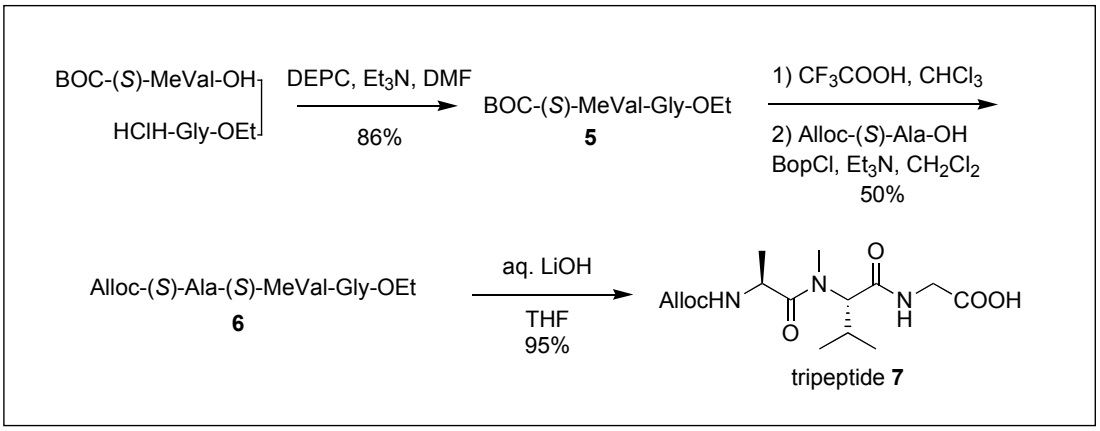
Fig. 1-1

1.2 Previous Synthetic Studies

Being a molecule with unique biological activities and structural complexities, antillatoxin has been the target of much synthetic endeavours. In 1998, Shioiri and co-workers accomplished the first total synthesis of (4*S*, 5*R*)-antillatoxin with the proposed structure **4a**.[7a]

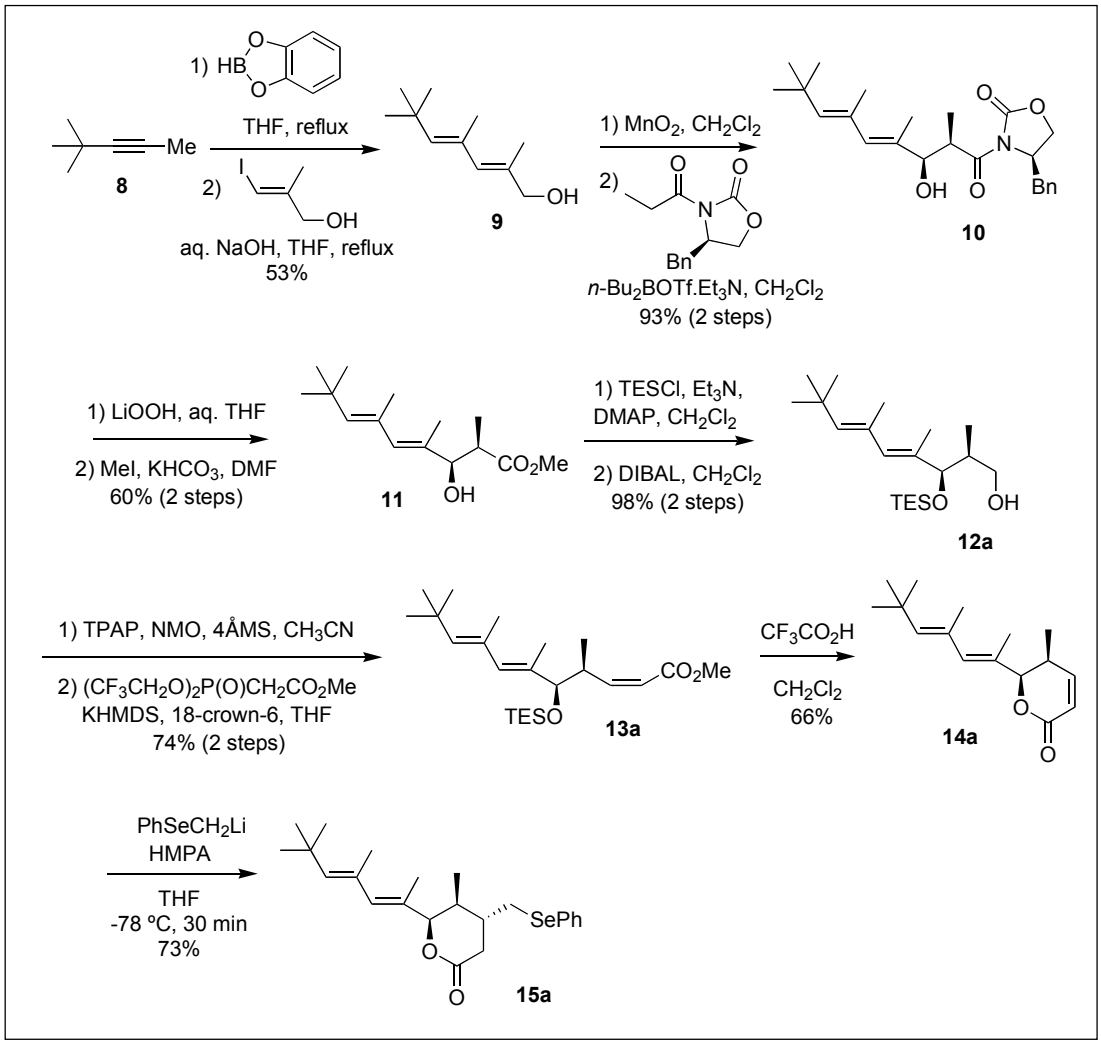
[7a] Yokokawa, F.; Shioiri. T. *J. Org. Chem.* **1998**, *63*, 8638-8639.

From their synthetic strategy, the complex molecule was constructed from two subunits, a tripeptide unit and a diene fragment (Scheme 1-1, 1-2, 1-3). The tripeptide unit **7** was prepared from alkaline saponification of **6** after a series of peptide coupling reaction as shown in Scheme 1-1.



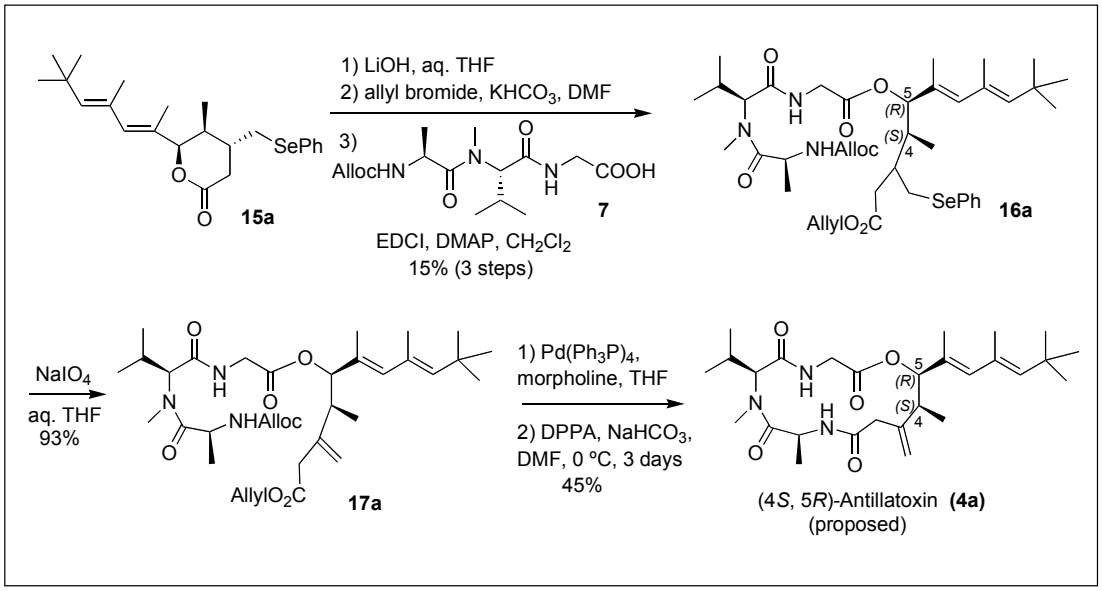
Scheme 1-1

Preparation of diene fragment **15a** was achieved from alkyne **8** as the starting material as shown in Scheme 1-2. The conjugated diene **9** was made from hydroboration of alkyne **8** followed by Suzuki coupling with vinyl iodide. Evans' chiral auxiliary was applied to generate the chiral centers at C_4 and C_5 of intermediate **10**.



Scheme 1-2

Lactone ring opening of **15a** followed by allyl protecting and esterification with tripeptide **7** gave the coupling product **16a**. Oxidative elimination of the phenylselenyl group, removal of allyl protecting groups and a final macrolactamization gave the desired macrocycle antillatoxin **4a**. (Scheme 1-3)



Scheme 1-3

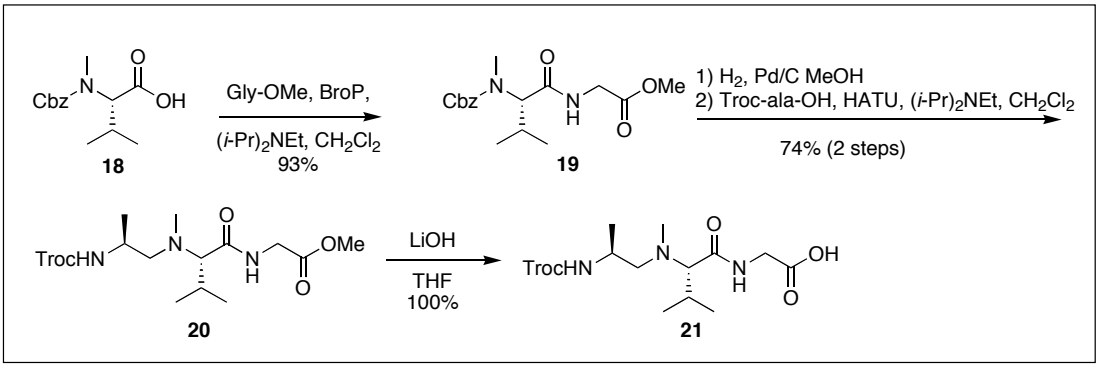
Gerwick used NOE to confirm the stereochemistries of C_4 and C_5. In our group, we have been working on the synthesis of the isomers of C_4 and C_5 as NOE studies of large rings is known to be unreliable.[9]

Later, the NMR data of the synthetic (4*S*, 5*R*)-antillatoxin (**4a**) showed significant differences from the natural product. These differences led to the conclusion that the proposed structure does not accurately reflect the natural antillatoxin that was isolated by Gerwick and co-workers. On the basis of the assumption that the stereochemistries of the amino acids are secure, the stereochemistry at C_4 and C_5 would be doubtful.

Furthermore, Whites and co-workers (1999)[8] reported their work on total synthesis of (4*S*, 5*R*)-antillatoxin (**4a**). Their results were also consistent with the results reported by T. Shioiri's.

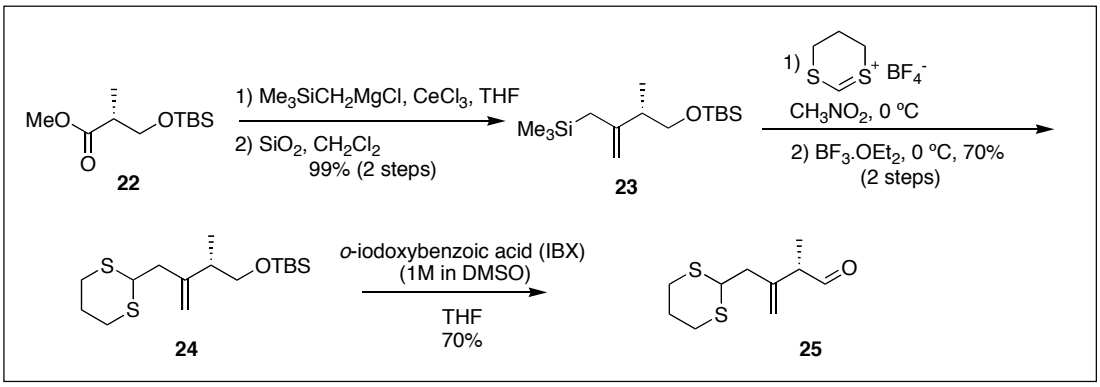
[9] Cao Guo-Qiang, PhD Thesis, **1998**.

Similar to Shioiri's strategy, the tripeptide unit **21** was prepared from the coupling of Cbz-protected N-methyl valine **18**, methyl glycine and Troc-protected alanine followed by LiOH saponification as shown in Scheme 1-4.



Scheme 1-4

The aldehyde **25** was constructed from an optically pure methyl propionate **22** *via* a series of transformations as shown in Scheme 1-5.

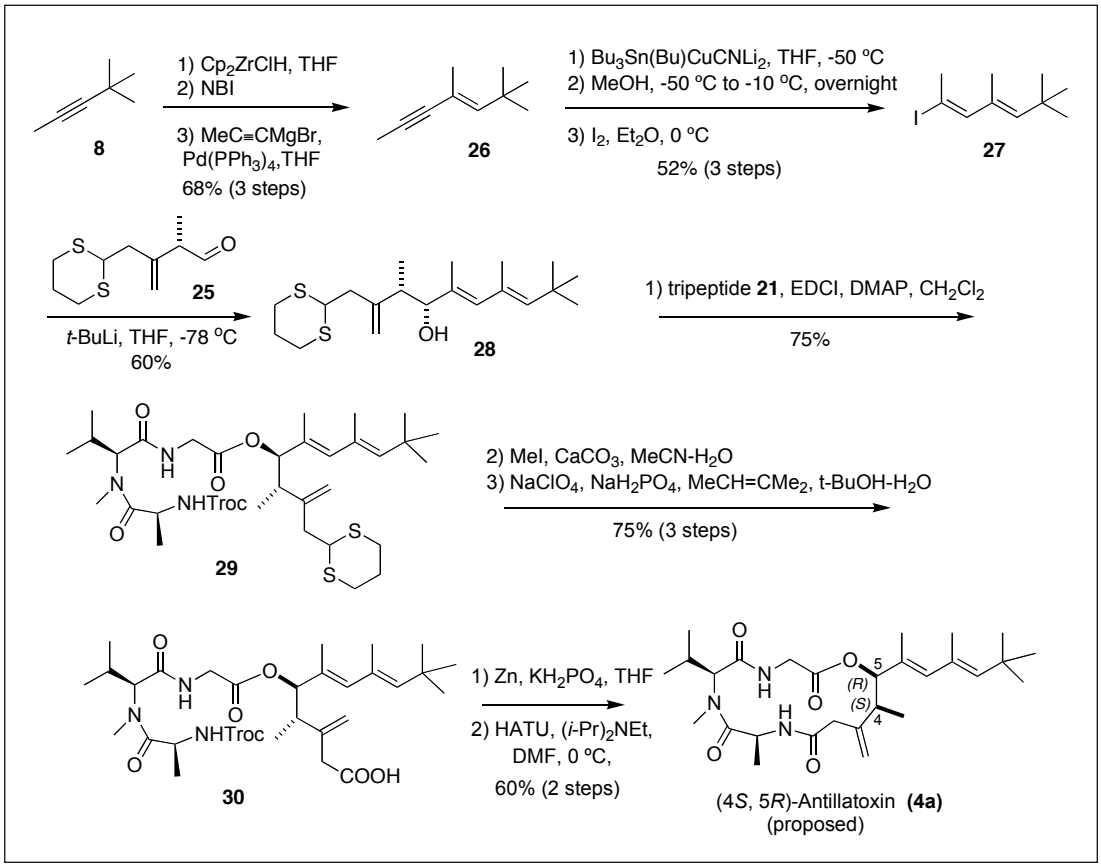


Scheme 1-5

Coupling of aldehyde **25** with diene **27** (synthesized from alkyne **8**) gave the diene fragment **28**. Esterification of **28** with tripeptide **21** with EDCI provided the

[8] White, J. D.; Hanselmann, R.; Wardrop, D. *J. Am. Chem. Soc.* **1999**, *121*, 1106-1107.

coupling product **29**. Removal of dithiane, oxidation followed by Troc-deprotection and final macrolactamization led to antillatoxin **4a**. (Scheme 1-6)

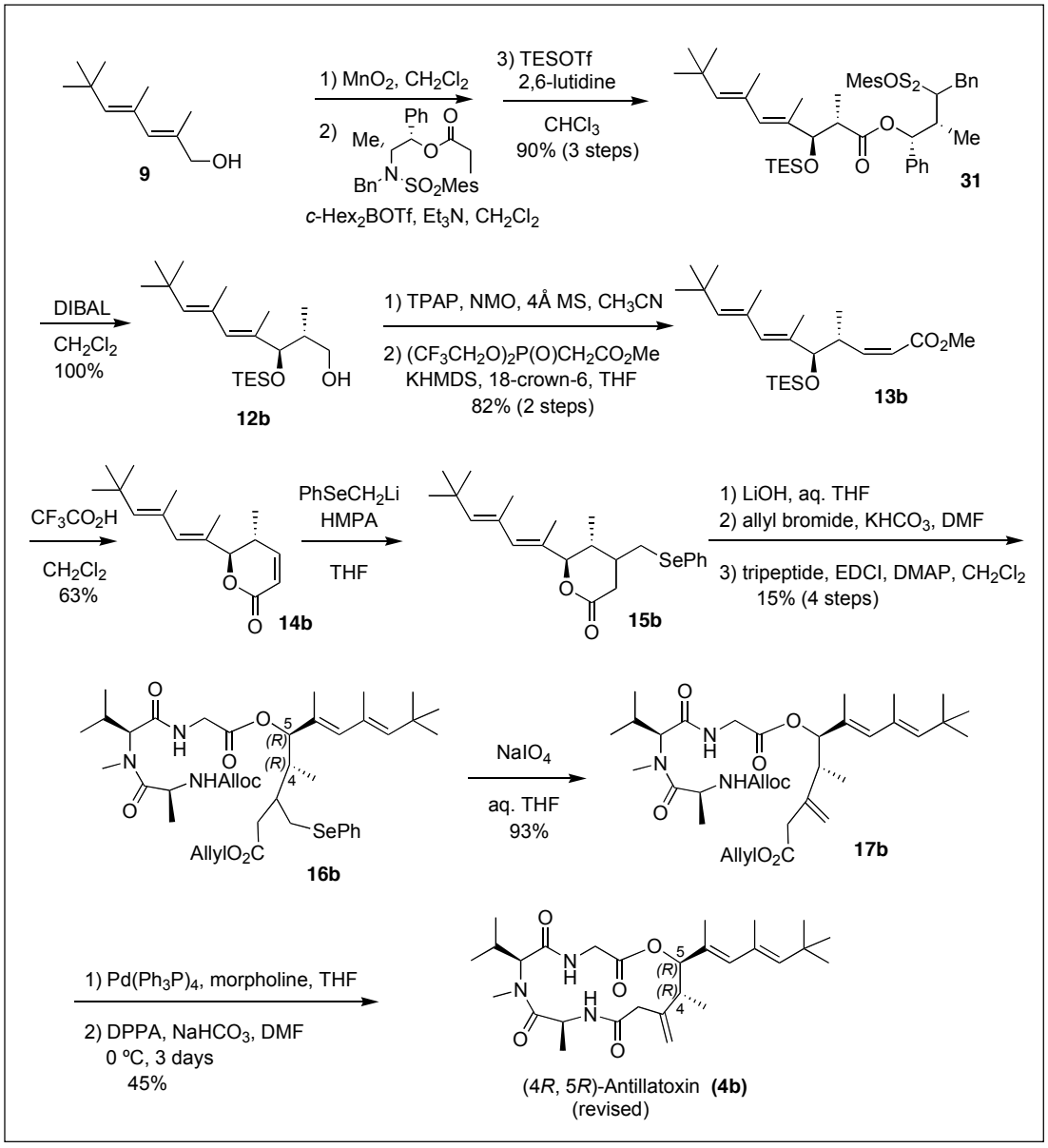


Scheme 1-6

From the analysis of the results obtained, Shioiri's group[7b,7c] has finally demonstrated that the correct structure should be (4*R*, 5*R*) *anti* configuration and not the proposed (4*S*, 5*R*) *syn* configuration. This was further confirmed by their synthesis of the (4*R*, 5*R*)-antillatoxin. In this new route, boron-mediated asymmetric aldol reaction was employed to construct the *anti*-C_4, C_5 configurations (Scheme 1-7). It was found that the resulting product was identical to the natural antillatoxin by comparing NMR, IR and optical rotation data. These series of work demonstrated that

[7b,7c] (b)Yokokawa, F.; Fujiwara, H.; Shioiri. T. *Tetrahedron Lett.* **1999**, *40*, 1915-1916. (c) Yokokawa, F.; Fujiwara, H.; Shioiri. T. *Tetrahedron* **2000**, *56*, 1759-1775.

the actual structure of antillatoxin should be revised to the (4*R*, 5*R*) configuration instead of the proposed (4*S*, 5*R*) configuration.



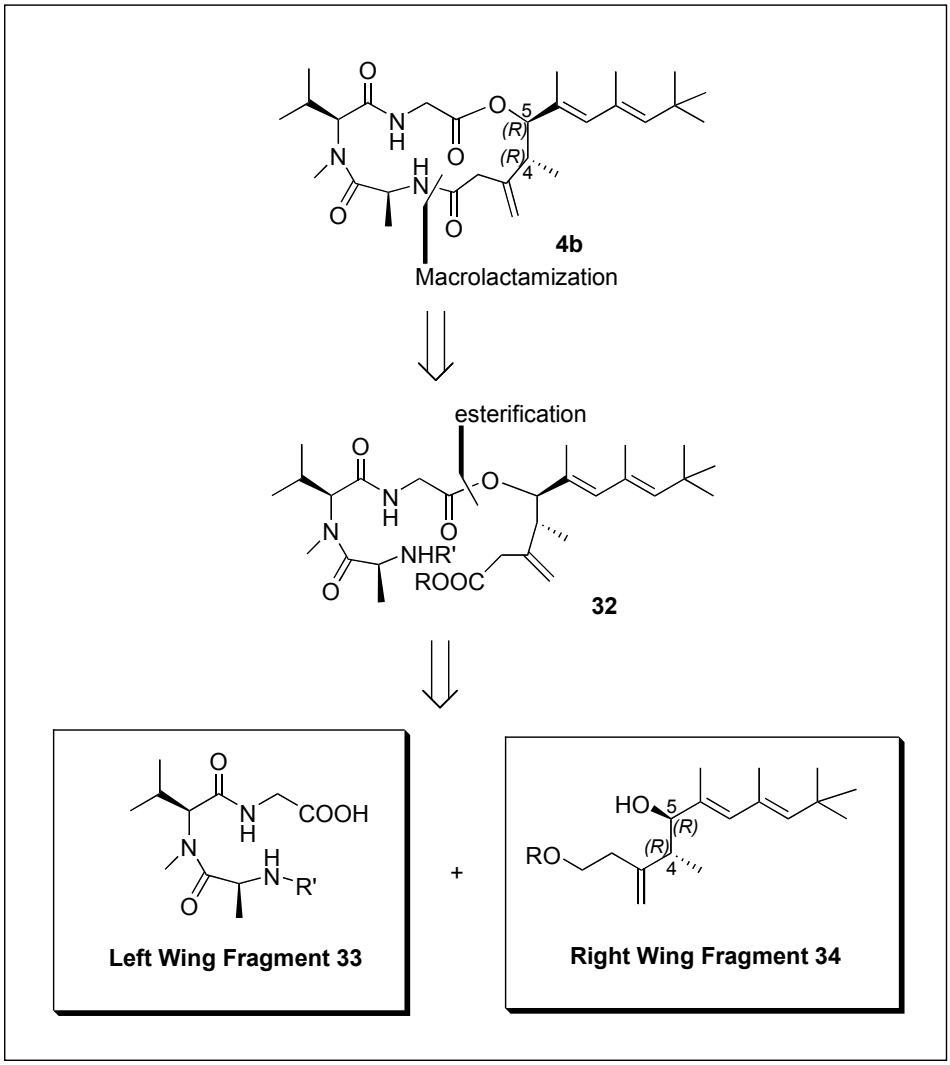
Scheme 1-7

Although White's and Shioiri's group have successfully synthesized antillatoxin, their synthetic routes are still long and cumbersome. Our strategy is to devise a short and efficient synthetic route to antillatoxin. Hopefully our synthetic route to antillatoxin will provide enough material for chemical and pharmacological

evaluation. With this in mind, our group embarked on the total synthesis of antillatoxin and its analogues.

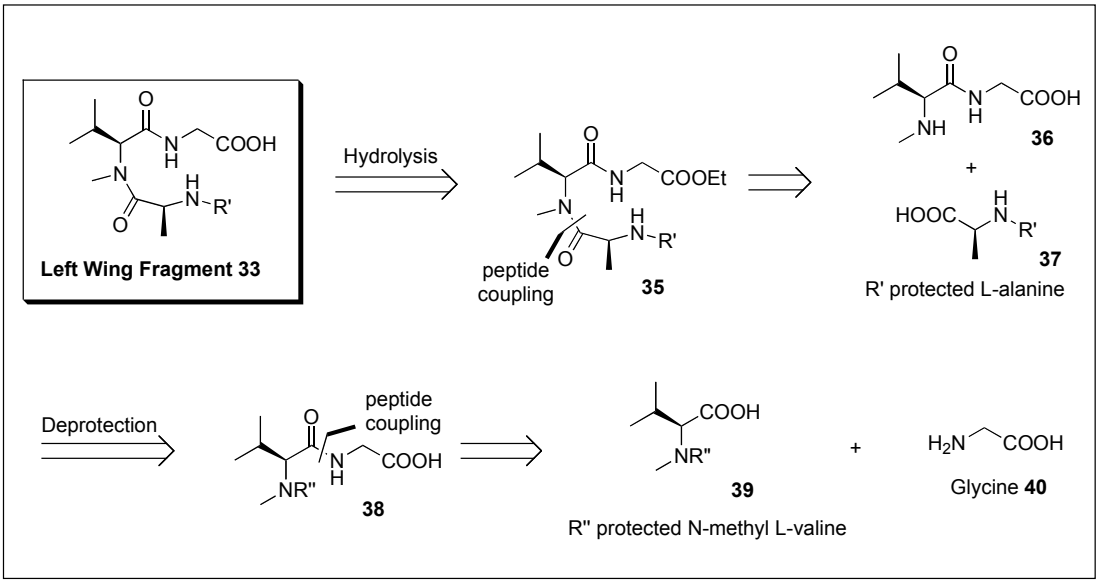
1.3 Our Retrosynthetic Analysis of Antillatoxin

Our retrosynthetic strategy of (4*R*, 5*R*)-antillatoxin **4b** is outlined in Scheme 1-8. Disconnection of the macrocycle ring using the macrolactamization strategy will give rise to precursor **32**. Retrosynthetic cleavage of the ester bond will lead to two key intermediates, the left wing fragment **33** and right wing fragment **34**.



Scheme 1-8

The tripeptide fragment **33** can be obtained from the coupling of three amino acids (N-methyl-L-valine (**39**), glycine (**40**) and L-alanine (**37**)) through a series of functional group manipulations using well established peptide chemistry.

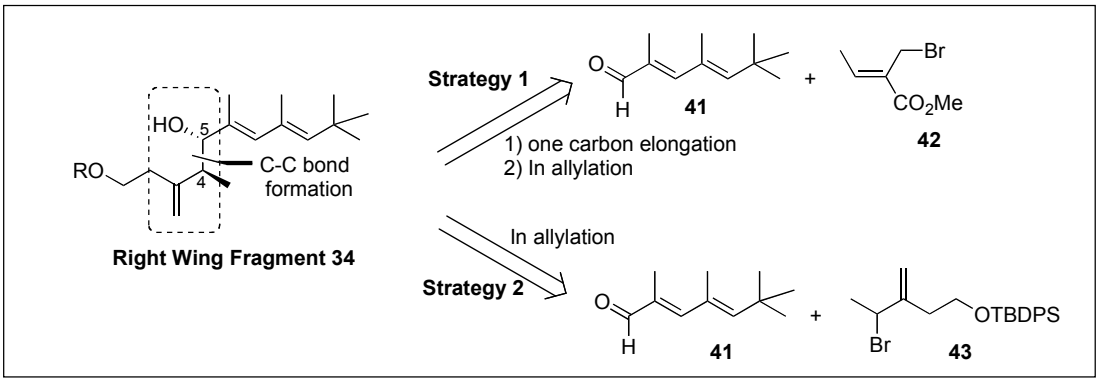


Scheme 1-9

The right-wing fragment **34** contains a homoallylic alcohol fragment which can be disconnected using a metal-mediated allylation strategy (Scheme 1-10). We decided to investigate the use of indium-mediated allylation strategy to carry out this transformation in aqueous media. The many advantages of carrying out reaction in aqueous media have encouraged us to investigate this transformation reaction on our system. Especially noteworthy is the possibility of avoiding protection-deprotection sequences such as hydroxy group in organic synthesis. This will shorten the required synthetic steps. Furthermore, it also enables large scale production, whereby the need to carry out the experiment under strictly anhydrous conditions can be avoided.

However, when we started this project, the scope and limitations of this reaction have not been well investigated. It is not known whether this reaction will work with a conjugated aldehyde, not to mention the possibility of 1,2 vs 1,4 vs 1,6 attack. Furthermore, the diastereoselectivity studies have not been well established and there was no study on the enantioselective version of this reaction.

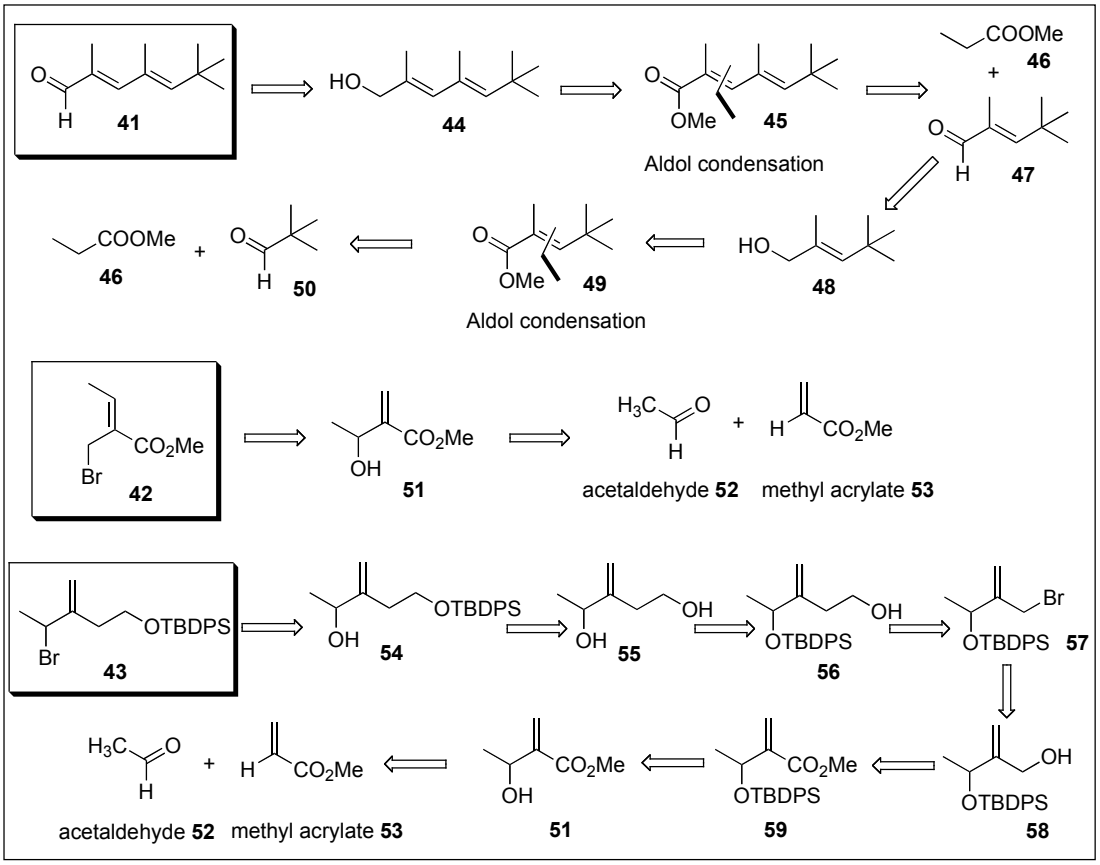
Two strategies have been proposed as shown in Scheme 1-10. In strategy 1, it is envisaged that the homoallylic alcohol **34** can be obtained from the indium-mediated allylation reaction of aldehyde **41** and β-substituted bromide **42** to generate the two new chiral centers at C_4 and C_5. It was then followed by one-carbon elongation to the proposed **34**. Strategy 2 proposed that fragment **34** could be formed from the indium-mediated allylation reaction of aldehyde **41** and secondary allylic bromide **43**.



Scheme 1-10

The key elements needed in the preparation of fragment **34** are depicted in Scheme 1-11. The methylated and conjugated aldehdye **41** could be derived from a series of aldol condensations, reductions and oxidations of the commercially available trimethylacetaldehyde **50** with methyl propionate **46**. Meanwhile, the bromides

synthon **42** and **43** can be made from the Baylis-Hilman reaction of acetaldehyde **52** and methyl acrylate **53** followed by a series of functional group interchanges.



Scheme 1-11

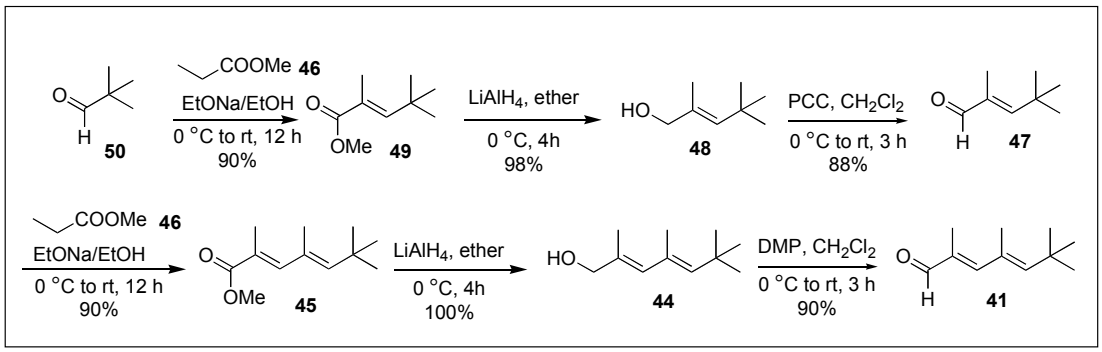
The crafted synthetic plan of antillatoxin focuses on the control of the pivotal chiral centres at C_4 and C_5. In addition, our strategy aims to realize the molecule through linking small and highly functionalized fragments. This would potentially allow our route to be easily adapted to the synthesis of analogs for pharmacological studies.

1.4 Results and Discussion

1.4.1 Synthesis of (2*E*, 4*E*)-2,4,6,6-tetramethyl-hepta-2,4-dienal (41)

Aldehyde **41** was synthesized from the commercially available trimethylacetaldehyde **50** through a series of aldol condensation reactions involving methyl propionate **46** (Scheme 1-12).

The aldol condensation of methyl propionate **46** with trimethylacetaldehyde **49** was carried out in the presence of 1.1 equivalent of sodium sand and catalytic amount of absolute ethanol at 0 °C for 2 hours to provide ester **49** in 90% yield. Reduction of methyl ester **49** with 2 equivalents of $LiAlH_4$ in ether at 0 °C afforded **48** in quantitative yield. Further oxidation of the alcohol **48** with pyridinium chlorochromate (PCC) in dichloromethane at 0 °C gave **47** in 88% isolated yield. Subsequently, repeating the aldol condensation of aldehyde **47** with methyl propionate **46** under the same condition mentioned above furnished **45** in 90% yield. This was followed by reduction ($LiAlH_4$) and oxidation (DMP) to give the aldehyde **41** in 90% yield (2 steps).



Scheme 1-12

The stereochemistry of aldehyde **41** was verified by NOE studies (Figure 1-2). From the spectrum, a strong NOE (10.7%) was observed between the aldehyde proton (9.37 ppm) and β proton (5.85 ppm). Another strong NOE (6.36%) observed between β proton (5.85 ppm) and proton at 6.68 ppm. A small NOE correlation (1.81%) was also observed between α and γ methyl groups. The correlations verified that the aldehyde **41** was of the *E*, *E* configuration.

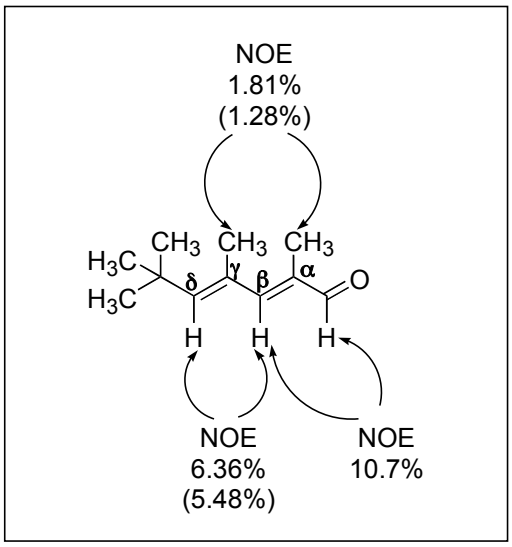
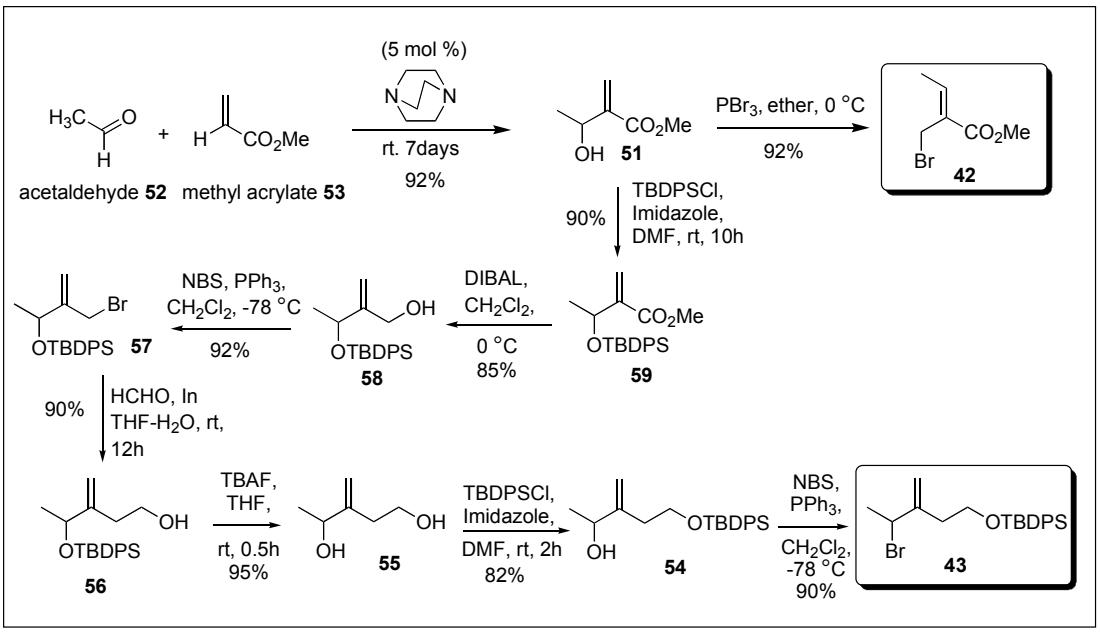


Figure 1-2

1.4.2 Synthesis of β-substituted Allylic Bromide 42 and Secondary Allylic Bromide 43

With building block aldehyde **41** in hand, we turned our attention to the synthesis of the allylic bromides **42** and **43** (Scheme 1-13). Both **42** and **43** were prepared from commercially available acetaldehyde **52** and methyl acrylate **53**. The coupling reaction between the two starting materials in the presence of catalytic amount of DABCO at room temperature for 7 days gave **51** in 92% yield. Subsequent bromination of **51** with PBr_3 in anhydrous ether at 0 °C give bromide **42** as a single

isomer in 92% yield. On the other hand, bromide **43** can be derived from **51** after a series of functional group manipulations. TBDPS protection of secondary alcohol of **51**, followed by DIBAL reduction of the ester group and NBS bromination gave the bromide **57** in 71% yield (3 steps). Indium-mediated allylation of formaldehyde with **57** afforded alcohol **56**. Subsequently, desilylation using TBAF followed by selective TBDPS protection of the primary alcohol and final NBS bromination provided the desired bromide **43** in 70% yield (3 steps).

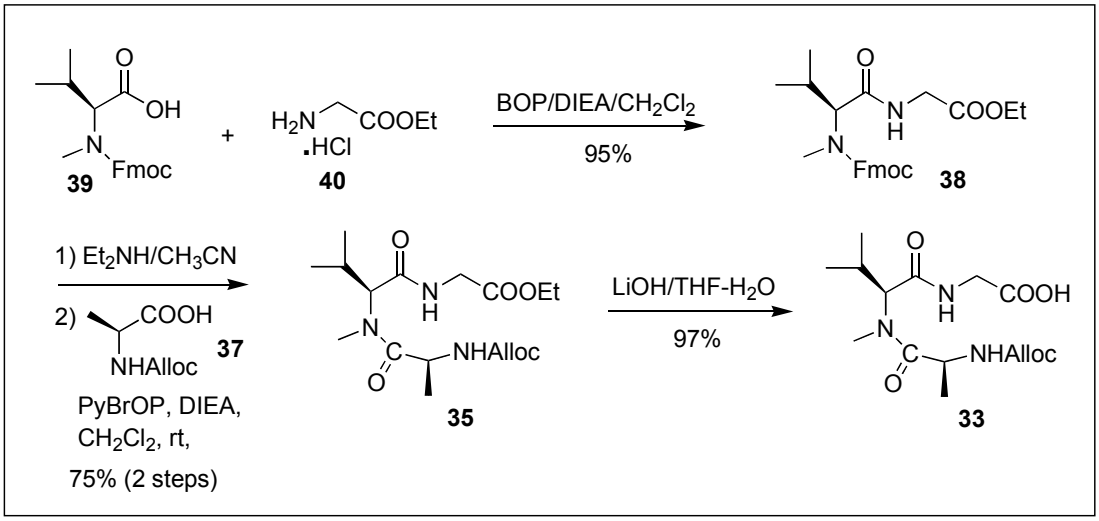


Scheme 1-13

1.4.3 Synthesis of Tripeptide Acid 33

Tripeptide acid **33** was prepared in 6 steps in high yield from three commercially available amino acids, Fmoc-*N*-methyl-L-valine, glycine and L-alanine

using the well-established peptide chemistry[10] (Scheme 1-14). Coupling of commercially available Fmoc-*N*-methyl-L-valine (**39**) with glycine ethyl ester (**40**) using benzotriazol-1-yloxytris (dimethylamino) phosphonium hexafluorophosphate (BOP) and diisopropylethylamine (DIEA) afforded the dipeptide **38** in excellent yield (95%). Removal of the Fmoc moiety of dipeptide **38** followed by coupling with alloc-L-alanine (**37**) in the presence of bromotripyrrolidinophosphonium hexafluorophosphate (PyBrOP) furnished the tripeptide ester **35** in 75% yield. Subsequent hydrolysis of the ethyl ester **35** using lithium hydroxide afforded the required tripeptide acid **33** as a single isomer without epimerization in 97% yield.



Scheme 1-14

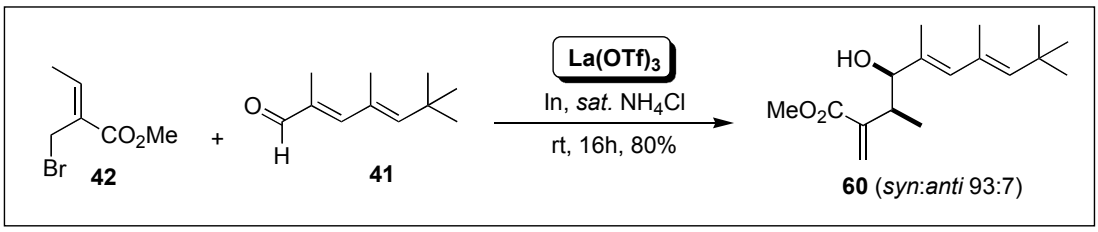
[10] Frerot, E.; Coste, J.; Pantaloni, A.; Dufour, M. N.; Jouin, P. *Tetrahedron* **1991**, *47*, 259. (b) Sennyey, G.; Barcelo, G.; Senet, J. P. *Tetrahedron Lett.* **1987**, *28*, 5809. (c) Castro, B.; Dormoy, J. R.; Evin, G.; Selve, C. *Tetrahedron Lett.* **1975**, *14*, 1219. (d) Li, K. W.; Wu, J.; Xing, W.; Simon, J. A. *J Am. Chem. Soc*. **1996**, *118*, 7237.

1.4.4 Synthesis of Fragment 34 Using Indium-Mediated Allylation

1.4.4.1 Synthesis of Fragment 65 - Strategy 1

With aldehdye **41** and two allylic bromides **42** and **43** in hand, we turn our attention to the indium-mediated allylation reaction between **41** and **42**, and between **41** and **43**, to produce the corresponding homoallylic alcohols.

In our efforts to develop environmentally friendly methodologies, our group has been involved in the pioneering work in the area of allyindium chemistry, particularly in aqueous media.[11] In our previous synthetic studies towards the total synthesis of antillatoxin, various conditions have been carried out. However in all cases, *syn* isomer was obtained as the major product.[12]



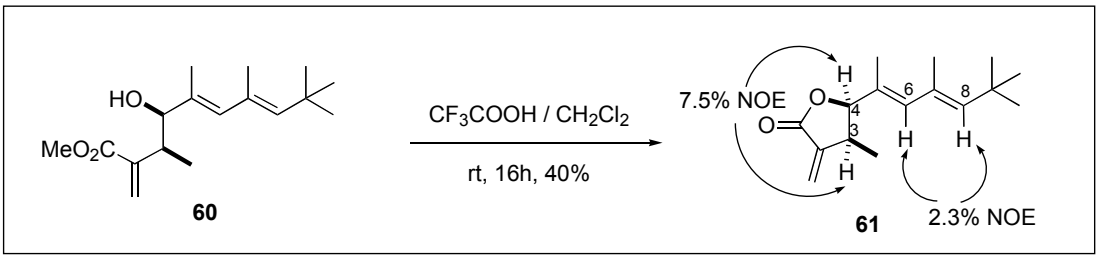
Scheme 1-15

Indium mediated allylation of the bromide **42** and aldehyde **41** was carried out in *sat*. NH_4Cl in the presence of indium powder and lanthanum triflate to give the homoallylic alcohol **60** in yields of 80% with high diastereoselectivity (*syn*/*anti* =

[11] (a) Wang, R.-B.; Lim, C. -M.; Tan, C. -H.; Lim, B. -K.; Sim, K. -Y.; Loh, T. -P. *Tetrahedron Asymmetry* **1995**, *6*, 1825. (b) Ho, D. S. -C.; Sim, K. -Y.; Loh, T. -P. *Synlett* **1996**, 263. (c) Li, X. -R.; Loh, T. -P. *Tetrahedron Asymmetry* **1996**, *7*, 1535.

[12] *Syn/anti* ratio was determined by comparing with the literature: Loh, T. -P.; Cao, G. -Q.; Pei, J. *Tetrahedron Lett.* **1998**, *39*, 1453.

93/7) (Scheme 1-15). Interestingly, when we performed the reaction in the absence of lanthanum triflate, no desired product was observed. Note that no 1,4-addition product was observed in this reaction, demonstrating the regioselectivity of this procedure. The stereochemical configuration of the *syn* isomer of homoallylic alcohol **60** was determined by the relatively intense NOE interaction exhibited by the lactone **61**, which was obtained by treating the homoallylic alcohol **60** with trifluoroacetic acid in CH_2Cl_2 at room temperature for 16 hours. Strong NOE between β and γ protons (NOE = 7.5%) was observed. This confirmed that the stereochemistry of the two chiral centers (C_3 & C_4) for the major product was *syn*. The NOE (2.3%) between protons on the conjugated double bonds (C_6 & C_8) further demonstrated that the conjugated double bond were in the *E*, *E* configuration (Scheme 1-16).[13]



Scheme 1-16

As an aside, Paquette's group[14] also reported the same observation as ours. It suggests that the allylindium intermediate coordinates with both the aldehyde carbonyl and the ester carbonyl functions as shown in Figure 1-3, leading to the *syn* adduct.

[13] Yin Zheng, PhD's thesis, **2000**.
[14] Paquette, L. A.; Rothaar, R. R. *J. Org. Chem.* **1999**, *64*, 217.

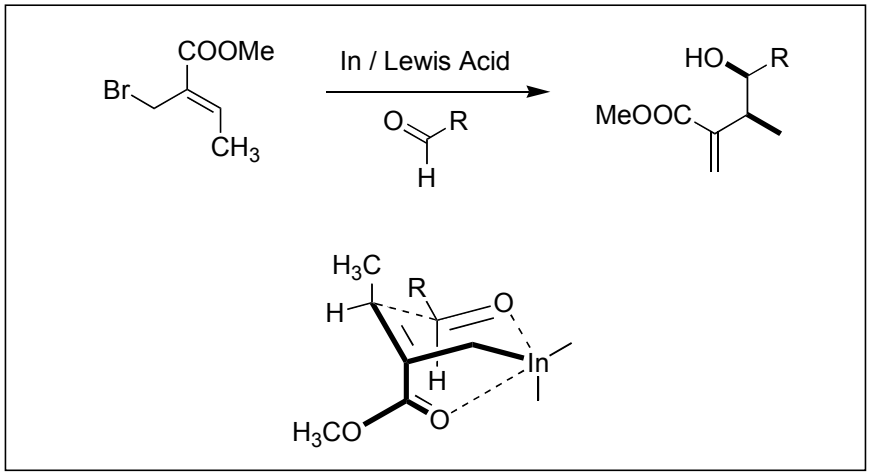


Figure 1-3

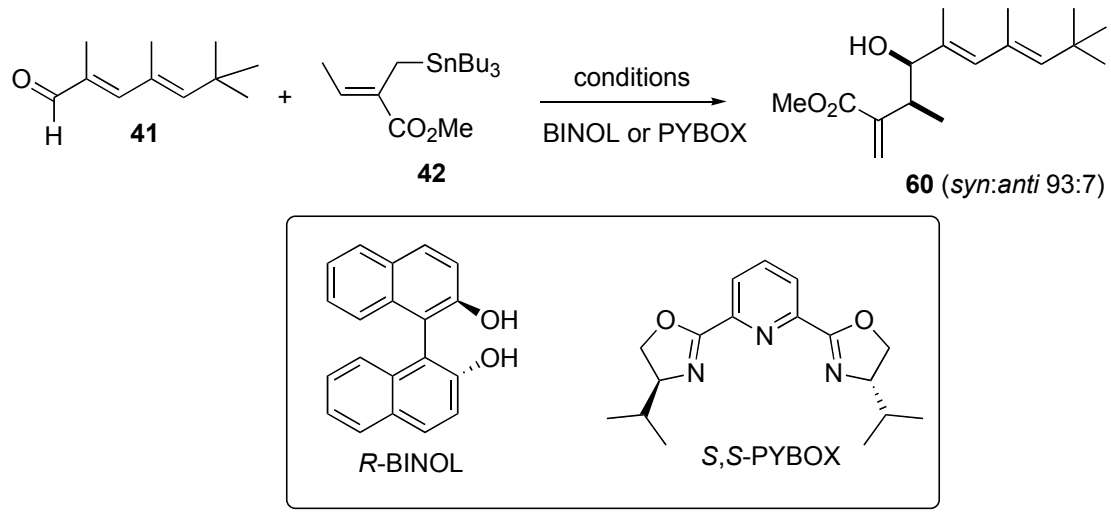
Apart form the above studies, the exploration of an enantioselective route to the preparation of homoallylic alcohol **60** was also carried out. Chiral ligand such as $InCl_3$-*R*-BINOL[15] and $In(OTf)_3$-PYBOX[16] were employed for controlling of the absolute stereochemistry. The results are summarized in Table 1-1.

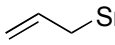
In general, chiral ligand-indium (III) complexes were formed *in situ* prior to the addition of ally tin **42** followed by the addition of aldehyde **41** under anhydrous condition in CH_2Cl_2 at -78 °C and slowly warming up to room temperature. The homoallylic alcohol obtained was predominantly in the *syn* configuration. These results are consistent with the earlier study by our group as discussed in the earlier section.

[15] (a) Teo, Y. -C.; Tan, K. -T.; Loh, T. -P. *Chem. Commun.* **2005**, 1318-1320. (b) Teo, Y. -C.; Loh, T. -P. *Org. Lett.* **2005**, *7*, 2539-2541. (c) Teo, Y. -C.; Goh, J. -D.; Loh, T. -P. *Org. Lett.*, **2005**, *7*, 2743-2745.

[16] (a) Lu, J.; Hong, M. -L.; Ji, S. -J.; Loh, T. -P. *Chem. Commun.* **2005**, 1010-1012. (b) Lu, J.; Ji, S. -J.; Teo, Y. -C.; Loh, T. -P. *Org. Lett.* **2005**, *7*, 159-161.

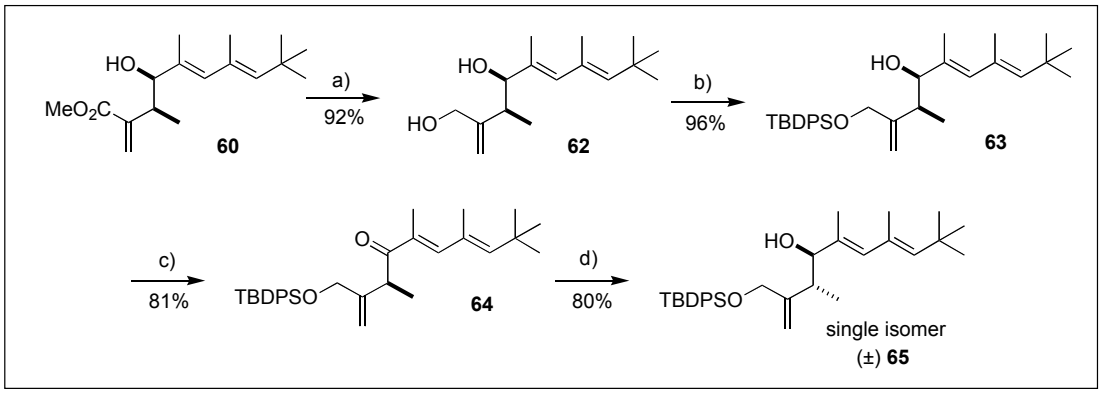
Table 1-1



Entry	Metal	Chiral ligand	Conditions	Yields
1	$InCl_3$	*R*-BINOL[15]	-78 °C	*syn* product, 75% no *ee*
2	$InCl_3$	*R*-BINOL	 SnBu3, -78 °C	*syn* product, 10% 8% *ee*
3	$In(OTf)_3$	*S,S*-PYBOX[16]	TMSCl, -78 °C	No reaction
4	$In(OTf)_3$	*S,S*-PYBOX	No TMSCl, -78 °C	No reaction

From the retrosynthetic analysis, the desired alcohol for the total synthesis of (4*R*, 5*R*) antillatoxin should be in *anti* configuration at the C_4 and C_5 chiral centers. However, the stereochemistry of the indium-mediated allylation reaction observed was in a *syn* configuration instead of the desired *anti* configuration in all cases.

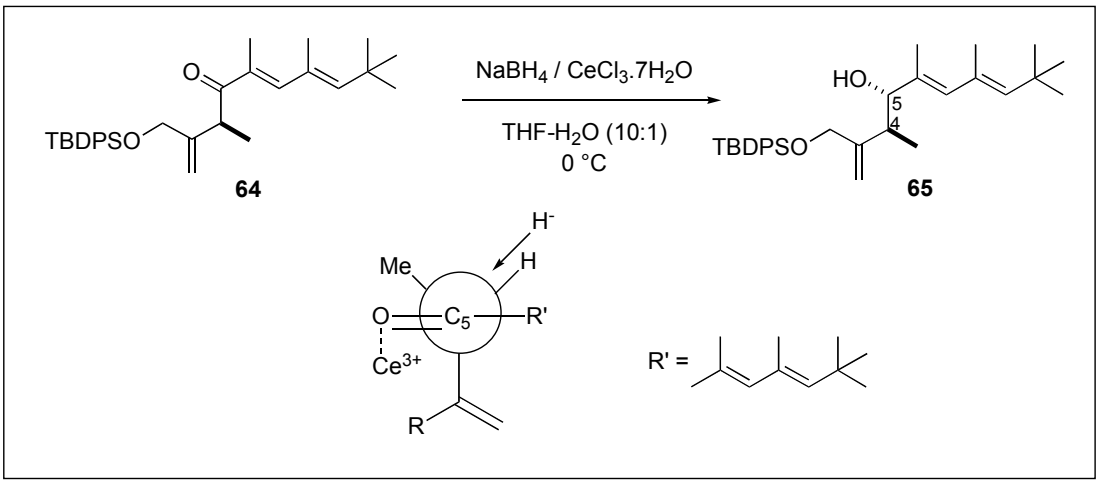
Therefore, we had to develop a new methodology to obtain the desired *anti*-isomer. In this case, oxidation followed by Luche's reduction[17] was employed in order to get the *anti* configuration. Initially, the *syn* allylation product **60** was reduced to diol **62** using DIBAL in CH_2Cl_2 as solvent. Selective protection of diol **62** with TBDPSCl in the presence of imidazole in DMF afforded **63**. The homoallylic alcohol **63** was then oxidized to **64** using Dess-Martin periodinane before it was subsequently reduced using $CeCl_3.7H_2O$ (1 equiv) and $NaBH_4$ (1 equiv) in a THF-H_2O (10:1) solution. The alcohol *anti*-**65** was obtained in 80% yield with excellent selectivity (*anti:syn* > 99:1). (Scheme 1-17)



Scheme 1-17 Reagents and conditions: a) DIBAL, CH_2Cl_2, 0 °C, 3h; b) TBDPSCl, Imidazole, DMF, 0 °C, 1.5h; c) Dess-Martin Periodinane, CH_2Cl_2, 0 °C, 3h; d) $NaBH_4$, $CeCl_3.7H_2O$, THF:H_2O (10:1), 0 °C, 3h.

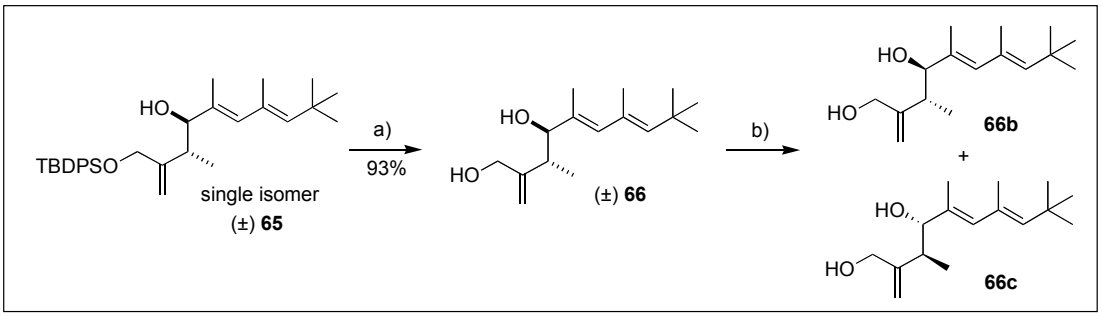
The preferred stereochemical course for the projected reduction can be rationalized using the Cram-Felkin-Anh model. The incoming hydride would approach the carbonyl group from the less hindered side and hence fashion the required *anti* relative stereochemistry (Scheme 1-18).

[17] Application of Luche's reduction in organic synthesis: Luche, J. L. *J. Am Chem. Soc.* **1978**, *100*, 2226-2227. (b) Loh, T. -P.; Hu, Q. -Y. *Org. Lett.* **2001**, *3*, 279-281.



Scheme 1-18

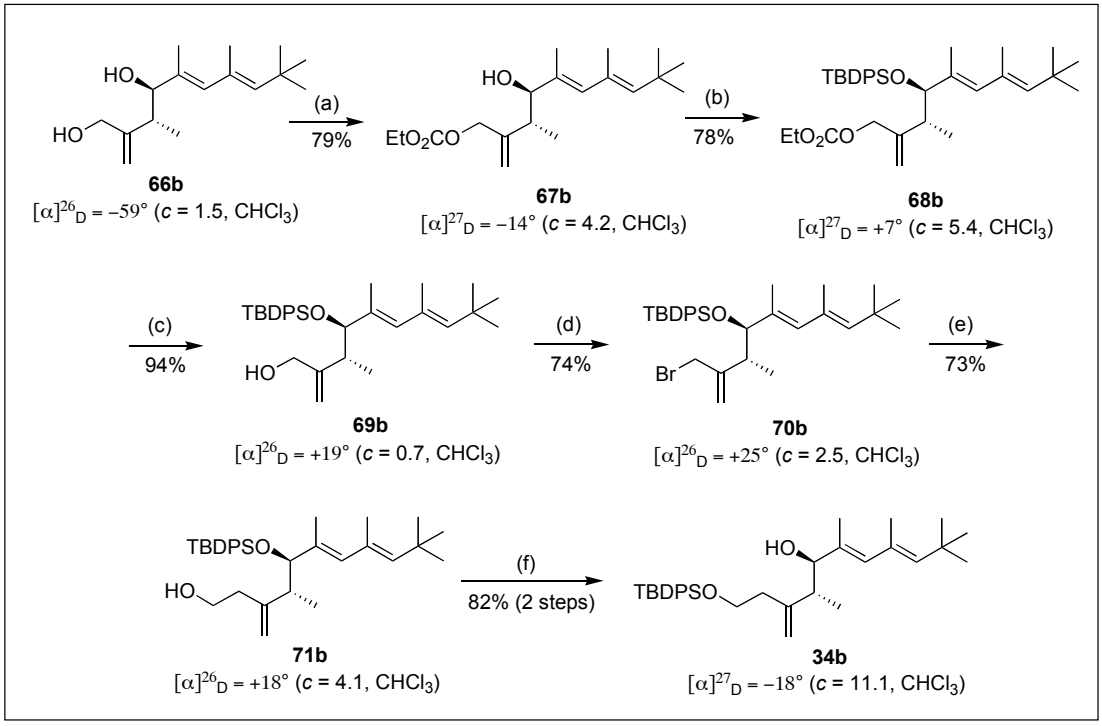
After furnishing the *anti* configuration of the alcohol **64**, our next task is to separate out both enantiomers to determine which enantiomer would lead to the natural (4*R*, 5*R*) antillatoxin. This was achieved by using chiral resolution with *S*-(+)-α-acetoxyphenylacetic acid (Scheme 1-19). In one of our first attempts, protection of the secondary alcohol of homoallylic alcohol **65** with *S*-(+)-α-acetoxyphenylacetic acid[18] in the presence of DCC, DMAP and molecular sieves was carried out. To our disappointment, the diastereomers cannot be separated using flash column chromatography.



Scheme 1-19 Reagents and conditions: a) TBAF, THF, rt; b) Chiral resolution of **66** was carried out with *S*-(+)-α-acetoxyphenylacetic acid followed by LiOH hydrolysis.[18]

[18] For the standard procedure, refer to Whitesell, J. K.; Reynolds, D. *J. Org. Chem.* **1983**, *48*, 3548.

In spite of our difficulties with the separation, we approached another alternative using *anti*-diol **66**, where both free alcohol in *anti*-diol **66** were protected with *S*-(+)-α-acetoxyphenylacetic acid. The *anti*-diol **66** was generated from desilylation of the TBDPS protecting group of homoallylic alcohol **65** with TBAF in THF as solvent (Scheme 1-19). The diastereomers were separated in pure form using an optimized solvent system (CH_2Cl_2:Hex:EA = 3:3:0.2). Enantiopure diol **66b** and **66c** were obtained after hydrolysis with LiOH in THF/H_2O (1:1).



Scheme 1-20 Reagents and conditions: a) EtOCOCl, DMAP, Et_3N, CH_2Cl_2, 0 °C to rt, 3h; b) TBDPSCl, $AgNO_3$, DMF, 0 °C to rt, 12h; c) 1% K_2CO_3 / MeOH, rt, 16h; d) NBS, PPh_3, CH_2Cl_2, - 78 °C to 0 °C, 3h; e) HCHO, In, $La(OTf)_3$, THF-H_2O (1:1), rt, 4 days; f) (i)TBAF, THF, rt; (ii) TBDPSCl, imidazole, DMF, 0 °C, 1.5h.

From the optically pure **66b**, one carbon elongation was performed to furnish the carbon backbone of the right wing fragment **34b** as shown in Scheme 1-20. First of all, we protected the primary alcohol with ethyl chloroformate in the presence of Et_3N and DMAP at 0 °C. Subsequently, the carbonate protected homoallylic alcohol

66b was treated with TBDPSCl in the presence of $AgNO_3$ in DMF at 0 °C and warmed to room temperature and stirred for 12 hours to afford the TBDPS group at the secondary alcohol in 78% yield. Consequently, the carbonate was cleaved selectively by basic hydrolysis using 1% K_2CO_3 methanol solution to afford the homoallylic alcohol **69b**. NBS bromination was carried out in the presence of PPh_3 in CH_2Cl_2 at -78 °C and warmed to 0 °C subsequently for 3 hours to provide the desired bromide **70b** in 74% yield.

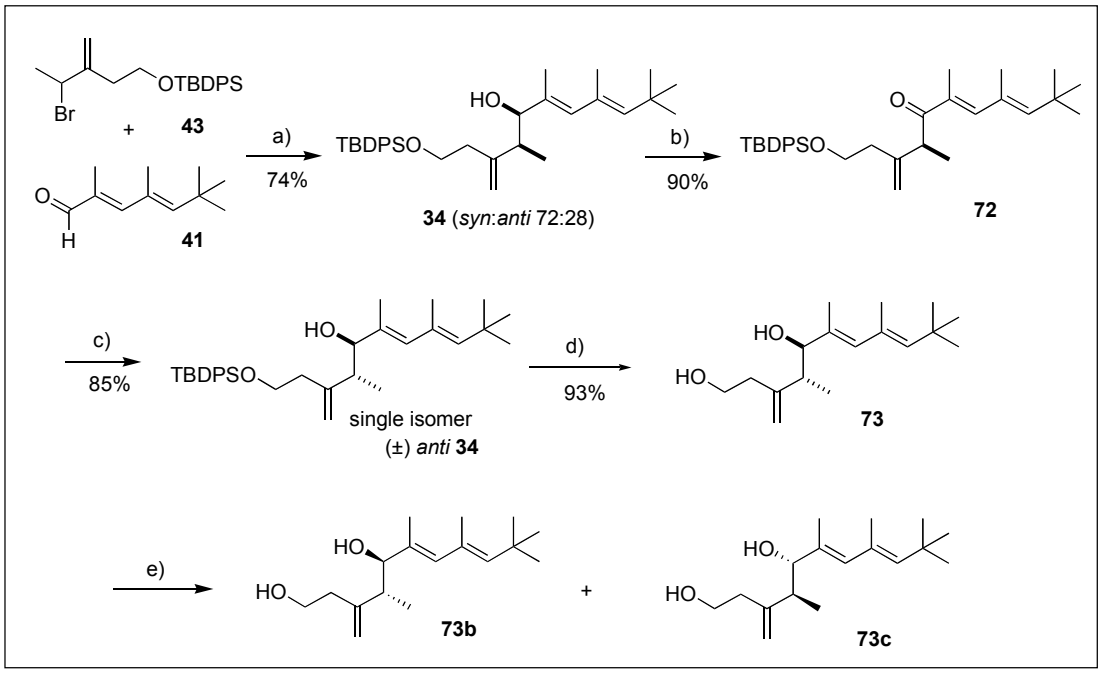
With the bromide **70b** in hand, our next target is to perform the one-carbon elongation to furnish the carbon backbone of the right wing fragment **34**. Using the conditions described by our group, this one-carbon elongation reaction proceeded smoothly using indium-mediated allyation of bromide **70b** with formaldehyde in the presence of $La(OTf)_3$ (1 equiv.) in THF-H_2O (1:1) at room temperature for 4 days to give the desired **71b** in 73% yield (Scheme 1-20).

Before we carried out the coupling between fragments **34** and **33**, the silicon protecting group was switched to primary position by deprotection of the secondary TBDPS protected alcohol followed by selective protection of the primary alcohol to furnish the fragment **34** for the next coupling reaction.

1.4.4.2 Synthesis of Fragment 65 - Strategy 2

In another synthetic route, indium mediate allylation with secondary allylic bromide **43** was also explored. Allylation reaction of the bromide **43** and aldehyde **41** in THF-H_2O in the presence of indium powder and lanthanum triflate gave the

homoallylic alcohol **34** in 74% yield with *syn*/*anti* selectivity at 72/28 (Scheme 1-21). Similar to the previous study, *syn* homoallylic alcohol was the major product instead of the *anti* configuration. In order to proceed with the synthetic study, the *syn* configuration was converted to *anti* using the same method described previously to afford the *anti*-**34**. Chiral resolution with *S*-(+)-α-acetoxyphenylacetic acid followed by primary TBDPS protection of **73b/73c** furnished the fragment **34b/34c** in optically pure form. (Scheme 1-21)



Scheme 1-21 Reagents and conditions: a) In, $La(OTf)_3$, THF-H_2O (1:1), rt, 16h; b) Dess-Martin Periodinane, CH_2Cl_2, 0 °C, 3h; c) $NaBH_4$, $CeCl_3.7H_2O$, THF:H_2O (10:1), 0 °C, 3h; d) TBAF, THF, rt; e) Chiral resolution of **73** was carried out with *S*-(+)-α-acetoxyphenylacetic acid followed by LiOH hydrolysis.[18]

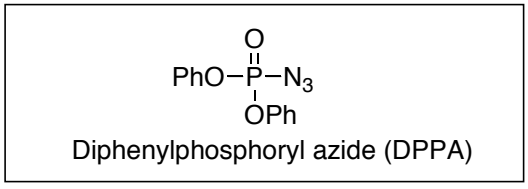
1.4.3 Coupling Between Fragment 33 and 34

With the pure *anti* homoallylic alcohol **34b/34c** and tripeptide acid **33** in hand, returned our attention to the union of these two advanced building blocks. As reported

in the earlier works by White's and Shiori's group,[4] coupling reagent 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (EDC.HCl) has been used to couple the two fragments. It had been shown that the reaction proceeded smoothly to give the product in good yield.

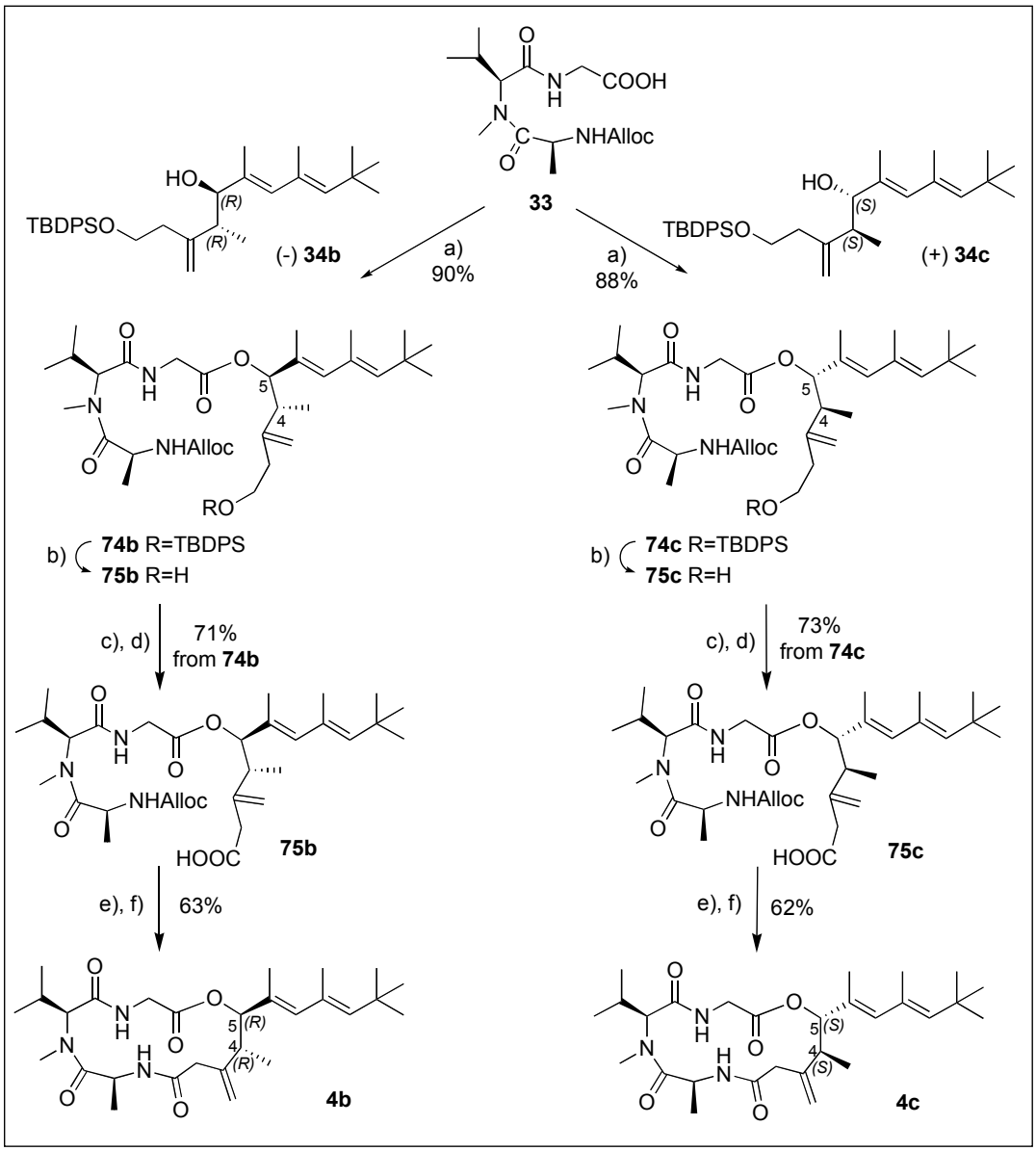
Using the same protocol, the homoallylic alcohol **34b** or **34c** was first mixed with 2 equivalents of tripeptide acid **33** in dried CH_2Cl_2 and cooled down to 0 °C in an ice bath. 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (EDC.HCl) and 4-dimethyl amino pyridine (DMAP) was added in one portion. The resulting mixture was stirred at 0 °C and slowly warmed to room temperature for 12 hours to give **74b/74c** in 90% and 89% yields respectively (Scheme 1-22).

With ample supplies of **74**, our next attempt was to free the functional groups needed to prepare **75**, the projected intermediate that may lead to the 15-membered macrocycle **4**. Deprotection of the silyl group with tetrabutyl ammonium fluoride (TBAF) followed by Dess-Martin and $NaClO_2$ oxidation afforded the corresponding acids **75b/75c** in 74% and 73% yields (3 steps reaction). Treatment of **75** with $Pd(PPh_3)_4$ in the presence of morpholine, followed by macrocyclization promoted by diphenyl phosphorazidate (DPPA)[19] gave (4*R*, 5*R*) antillatoxin (**4c**) and (4*S*, 5*S*) antillatoxin **(4b)** in 63% and 62% yields respectively. The product was confirmed by

19 

Diphenylphosphoryl azide (DPPA)

comparing the spectroscopic data of the synthetic sample with that of the natural product.[4,7]



Scheme 1-22: a) EDC.HCl, DMAP, CH_2Cl_2, 0 °C to rt, 16h; b) TBAF, THF, rt, 0.5h; c) Dess-Martin Periodinane, CH_2Cl_2, rt, 1h; d) $NaClO_2$, NaH_2PO_4, $MeCH{=}CMe_2$, *t*-BuOH-H_2O, rt, 1h; e) $Pd(Ph_3P)_4$, morpholine, THF, rt, 0.5h; f) DPPA, $NaHCO_3$, DMF, 0 °C, 3 days. [EDC.HCl = 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride; DMAP = 4-dimethyl amino pyridine; TBAF = tetrabutyl ammonium floride; DPPA = Diphenylphosphoryl azide]

[4] Orjala, J.; Nagle, D. G.; Hsu, V. L.; Gerwick, W. H. *J. Am. Chem. Soc.* **1995**, *117*, 8281-8282.

[7] (a)Yokokawa, F.; Shioiri. T. *J. Org. Chem.* **1998**, *63*, 8638-8639. (b)Yokokawa, F.; Fujiwara, H.; Shioiri. T. *Tetrahedron Lett.* **1999**, *40*, 1915-1916. (c) Yokokawa, F.; Fujiwara, H.; Shioiri, T. *Tetrahedron* **2000**, *56*, 1759-1775.

1.5 Biological Evaluation of Antillatoxin and Fragments Using Zebrafish Embryo

The recently established forward chemical genetics field has been gaining popularity and offers powerful tools to search for novel drug candidates and their targets.[20] It differs from classical genetics by substituting small molecules for mutation-inducing agents or X-ray irradiation. Using combinatorial techniques,[21] one is able to rapidly screen a large number of small molecules and identify those that induce a novel phenotype in a cellular or embryonic system. Once a phenotypic effect is found, the next step is to identify the biological target.

In the age of high-throughput biology, novel genes and proteins are emerging quickly. The need for developing organic synthesis-derived methods that allow rapid access to polyfunctional, complex natural product-like compounds is growing constantly, largely because these small-molecule-based compounds serve as smart, powerful tools both in understanding the roles and functions of emerging biological targets and in validating their biological responses.

Developing asymmetric synthesis-derived organic reactions allows the synthesis of complex natural product-like compounds in a high-throughput manner. With few exceptions, the synthesis of complex natural product-like derivatives is still in its infancy. Some recent efforts made in this area indicate opportunities yet to be explored. Zebrafish (*Danio rerio*) embryo screening offers a speedy method for the

[20] (a) Lokey, R. S. *Curr. Opin. Chem. Biol.* **2003**, *7*, 91-96. (b) Tan, D. S. *Nat. Biotechnol.* **2002**, *20*, 561-563. (c) Specht, K. M.; Shokat, K. M. *Curr. Opin. Cell Biol.* **2002**, *14*, 155-159. (d) Schreiber, S. L. *Chem. Eng. News* **2003**, March 3, 51-61.

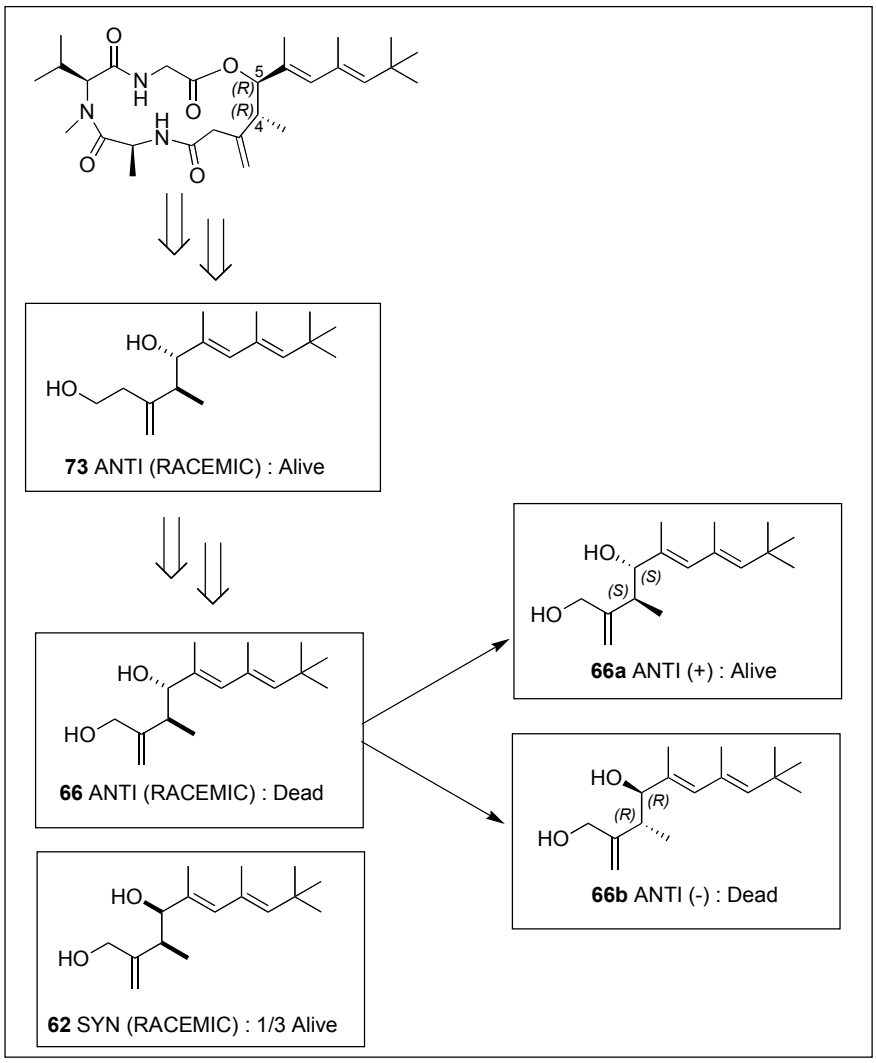
[21] (a) Jung, G. *Combinatorial chemistry: synthesis, analysis, screening*; Wiley-VCH: Weinheim; Cambridge, **1999**; (b) Nicolaou, K. C.; Hanko, R.; Hartwig, W. *Handbook of combinatorial chemistry: drugs, catalysts, materials*; Wiley-VCH: Weinheim, **2002**.

identification of compounds with interesting bioactivity. While the use of combinatorial methods has been extensively studied, the use of natural products and their analogs to search for more active compounds and their targets have attracted much less attention. Herein, we describe the utilization of a natural product which has known bioactivities, screening for unique phenotypical changes in the zebrafish embryo's development.

We envisage that the phenotype effects for a bioactive natural product can provide leads for the search of more bioactive compounds through seeking and cross-referencing the same phenotype(s) observed. This can be done using closely related analogs or simpler fragments of a specific natural product. Once an analog has been identified to cause similar phenotype effect(s), further biological studies will be carried out. This strategy of utilizing zebrafish embryo screening, will be able to provide a rapid route towards the synthesis of more potent targeted analogs in a shorter time. Application of this strategy has enabled us to identify specific activities of several fragments which are structurally related to the natural (4*R*, 5*R*)-antillatoxin (**4b**) we synthesized.

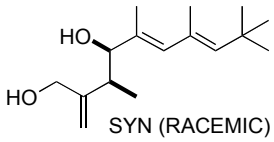
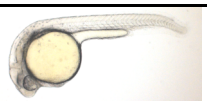
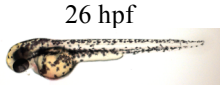
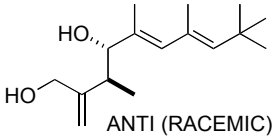
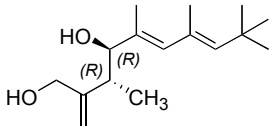
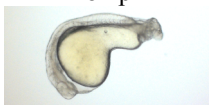
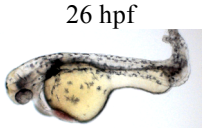
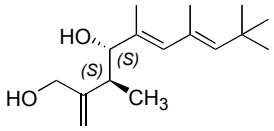
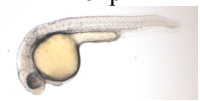
Screening of this library of simpler fragments obtained during the process of the total synthesis compounds has resulted in the discovery of potent compound. This simple screen utilizing zebrafish embryos (a three day monitoring, after post fertilization) followed by monitoring for any defects by visualization has resulted in the discovery of bioactive compound which has similar activity as (4*R*, 5*R*)-antillatoxin but with much simpler structure. Interestingly, although the *anti*-isomer (**66**) of the fragment afforded interesting activity, the *syn*-isomer (**62**) has no effect on

the zebrafish embryos (Scheme 1-23). Another noteworthy point is that only the enantiomer of the *anti*-isomer **66b** which corresponds to the natural product afforded the same phenotypes as the natural products. This shows that stereochemistry of this key fragment plays an important role in the activity. Furthermore, the 1-carbon elongated fragments (**73**) showed no effect on the zebrafish. Further testing further demonstrates the relationship between zebrafish embryos testing[21] and the ichthyotoxicity of the compound. The results of all different analogs are summarized in Table 1-2 and Table 1-3.

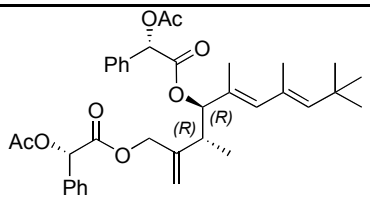
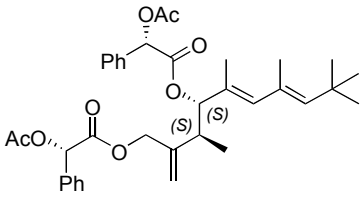
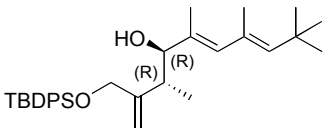
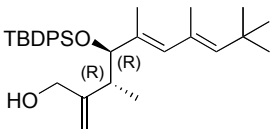
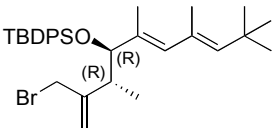
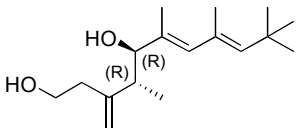
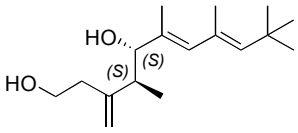
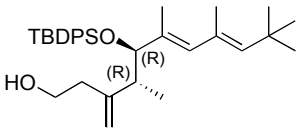
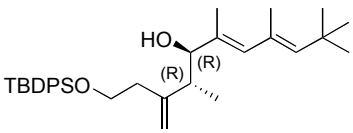
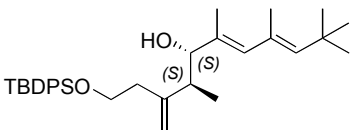


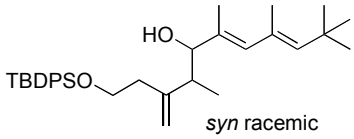
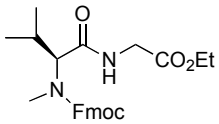
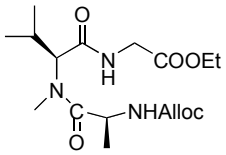
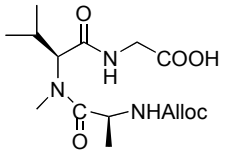
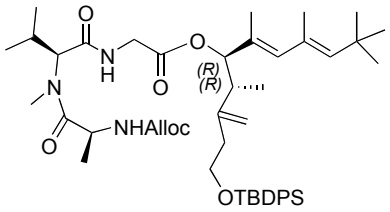
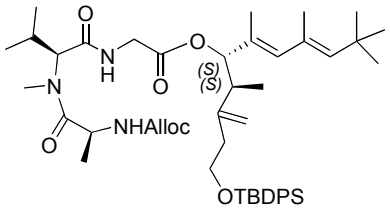
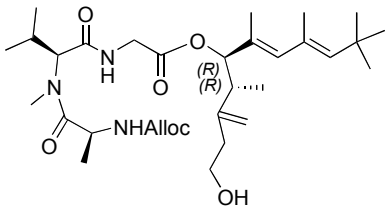
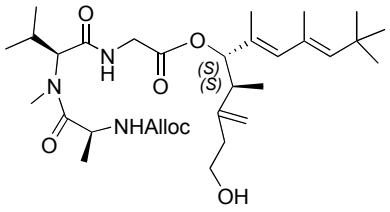
Scheme 1-23

Table 1-2 Phenotype screening[21] - antillatoxin and its fragments

Molecular Structure	Primary effect	Mark day	Lethal day	All general effect	Pictures
 SYN (RACEMIC)	-	1	-	-	 26 hpf  48 hpf
 ANTI (RACEMIC)	Specific issue	1	1	Notochord defect, vascular system	 26 hpf  48 hpf
	Specific issue	1	1	Notochord defect, vascular system	 26 hpf  48hpf
	-	1	-	No effect	 26 hpf  48 hpf

[21] Biological testing conducted by Ms. Wu Yilian (Phenotype screening) and IMA (Phenotype screening), Dr. K. N. Sulochana (Transgenic screening - GFP) and Dr. Farooq (Transgenic screening - GFP/RFP) in the Department of Biological Sciences, National University of Singapore.

Molecular Structure	Primary effect	Mark day	Lethal day	All general effect	Pictures
	-	-	-	No effect	-
	-	-	-	No effect	-
	-	-	-	No effect	-
	-	-	-	No effect	-
	-	-	-	No effect	-
	-	-	-	No effect	-
	-	-	-	No effect	-
	-	-	-	No effect	-
	-	-	-	No effect	-
	Motility	1	-	No effect	-

Molecular Structure	Primary effect	Mark day	Lethal day	All general effect	Pictures
	Motility	1	-	No effect	-
	Lethal	1	1	No effect	-
	-	-	-	No effect	-
	-	-	-	No effect	-
	-	-	-	No effect	-
	-	-	-	No effect	-
	-	-	-	No effect	-
	-	-	-	No effect	-

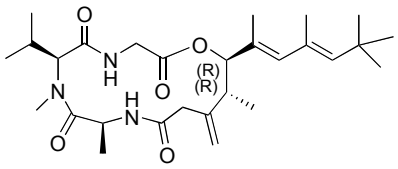
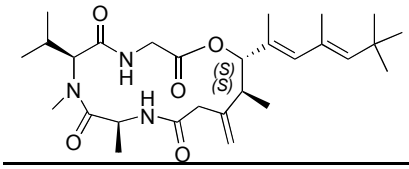
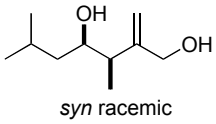
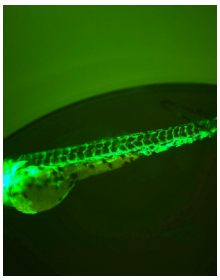
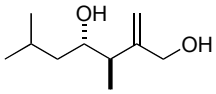
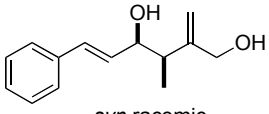
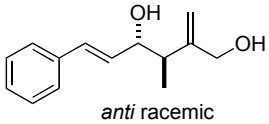
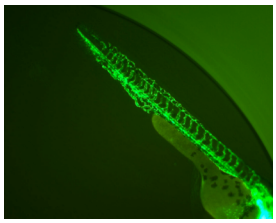
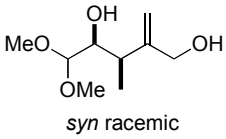
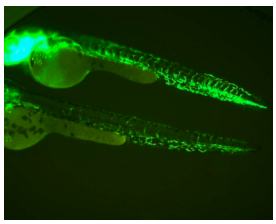
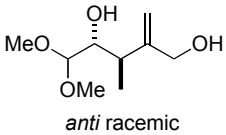
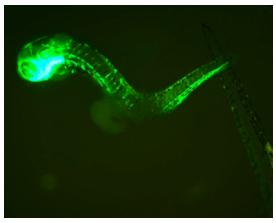
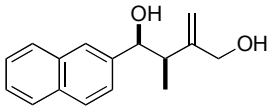
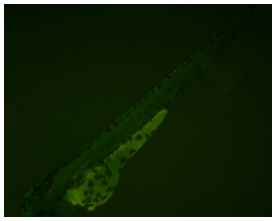
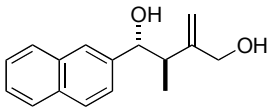
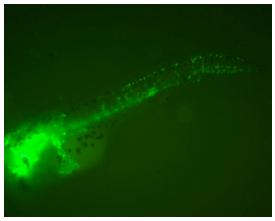
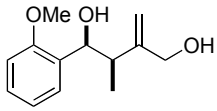
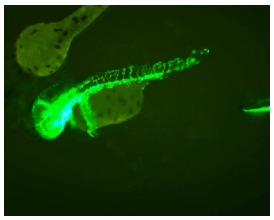
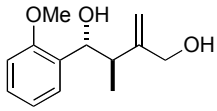
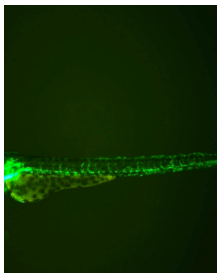
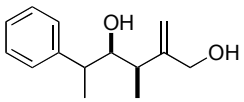
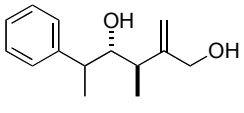
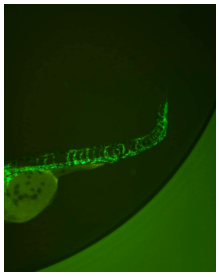
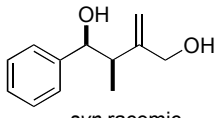
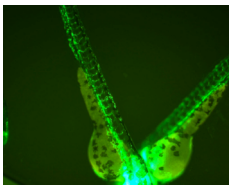
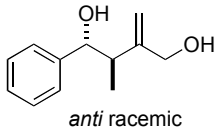
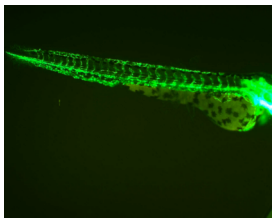
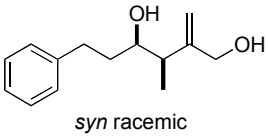
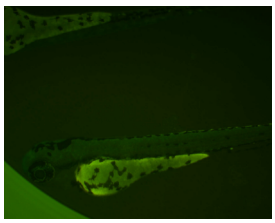
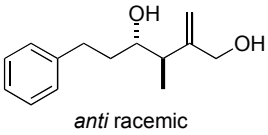
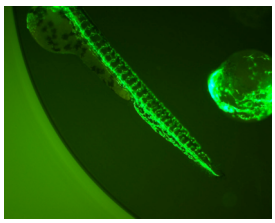
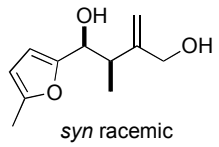
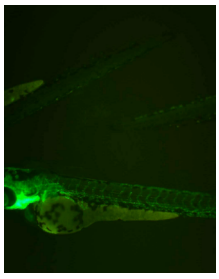
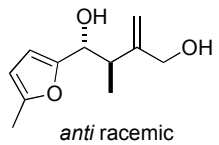
Molecular Structure	Primary effect	Mark day	Lethal day	All general effect	Pictures
	Specific issue	1	-	Heart, Notochord, Brain, Hatching gland, Vascular system	-
	-	-	-	No effect	-

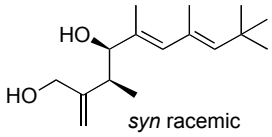
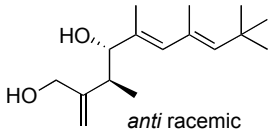
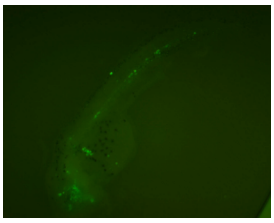
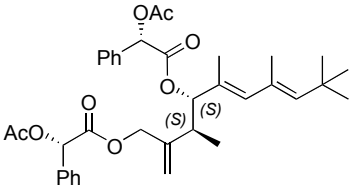
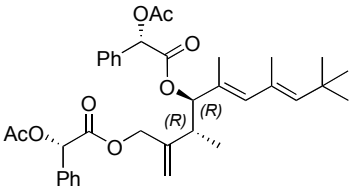
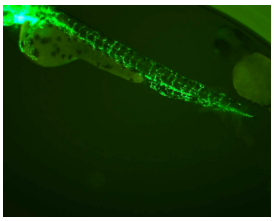
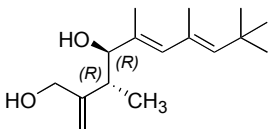
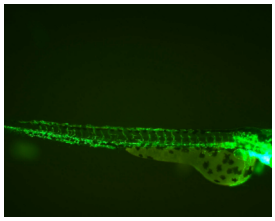
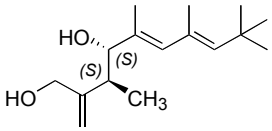
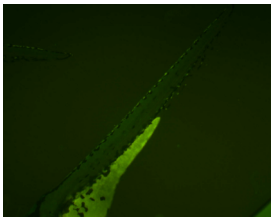
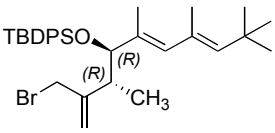
Table 1-3 Transgenic screening[21] - intersegmental vessels (ISV) effects caused by antillatoxin and its fragments

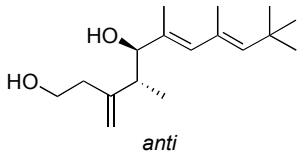
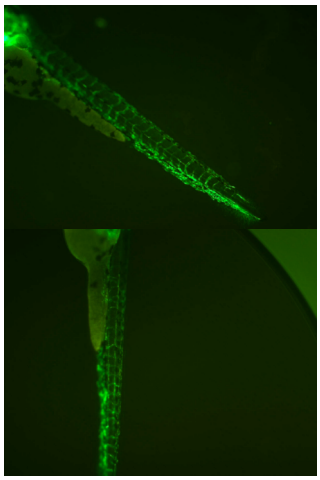
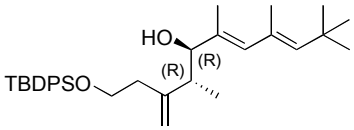
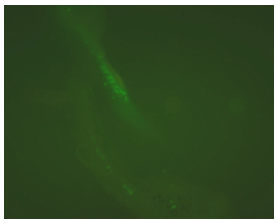
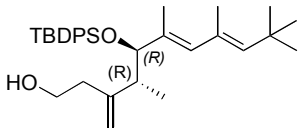
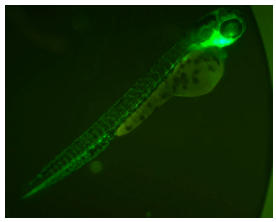
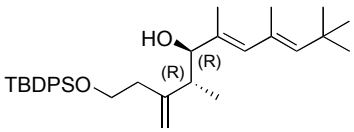
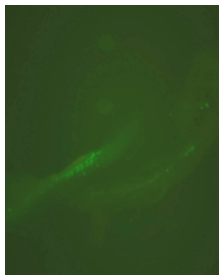
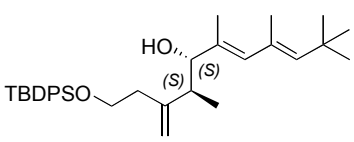
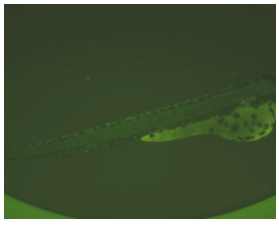
Molecular Structure	Primary effect	All general effect	Pictures
 *syn* racemic	ISV Over-expression	-	
 *anti* racemic	Normal development	-	-
 *syn* racemic	Normal development	-	-
 *anti* racemic	ISV Over-expression	-	
 *syn* racemic	ISV change	Anti-angiogenic effect	
 *anti* racemic	ISV change	Abnormal development, Notochord defect	

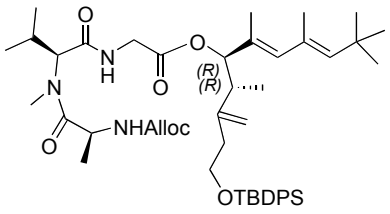
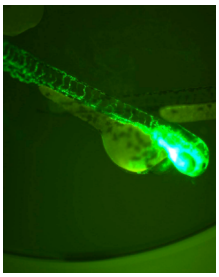
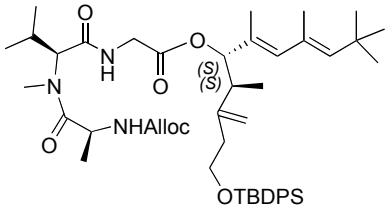
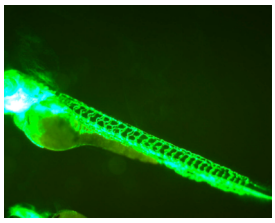
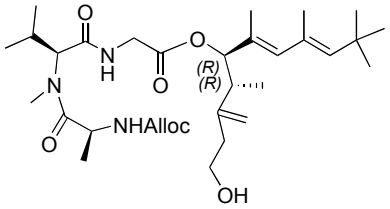
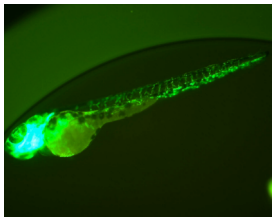
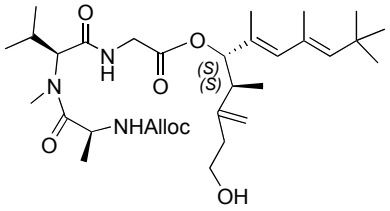
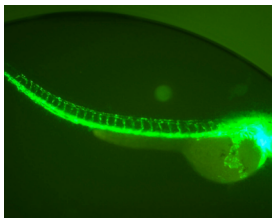
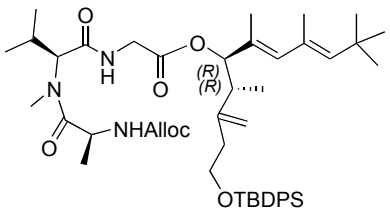
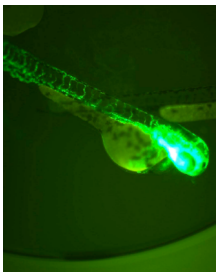
[21] Biological testing conducted by Ms. Wu Yilian (Phenotype screening) and IMA (Phenotype screening), Dr. K. N. Sulochana (Transgenic screening - GFP) and Dr. Farooq (Transgenic screening - GFP/RFP) in the Department of Biological Sciences, National University of Singapore.

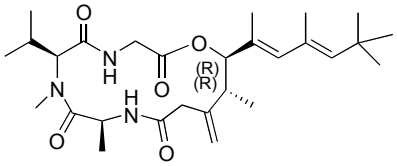
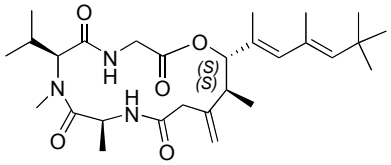
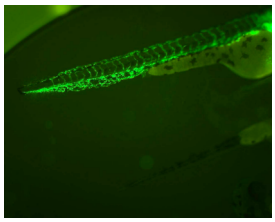
Molecular Structure	Primary effect	All general effect	Pictures
 *syn* racemic	ISV change	Anti-angiogenic effect	
 *anti* racemic	ISV change	Anti-angiogenic effect	
 *syn* racemic	ISV Over-expression	-	
 *anti* racemic	ISV change	Abnormal development	
 *syn* racemic	Normal development	-	-
 *anti* racemic	ISV change	Abnormal development	

Molecular Structure	Primary effect	All general effect	Pictures
 *syn* racemic	ISV change	Abnormal development	
 *anti* racemic	ISV Over-expression	-	
 *syn* racemic	ISV change	Anti-angiogenic effect	
 *anti* racemic	ISV Over-expression	-	
 *syn* racemic	ISV change	Weak development	
 *anti* racemic	Normal development	-	-

Molecular Structure	Primary effect	All general effect	Pictures
	Normal development	-	-
	ISV change	No circulation	
	Normal development	-	-
	ISV change	Abnormal development	
	ISV change	Abnormal development	
	ISV change	No circulation	
	ISV change	No circulation	

Molecular Structure	Primary effect	All general effect	Pictures
	ISV change	Abnormal development	
	ISV change	Abnormal blood vessel development, gross defect	
	Normal ISV	-	
	ISV change	-	
	ISV change	Abnormal blood vessel development, gross defect	

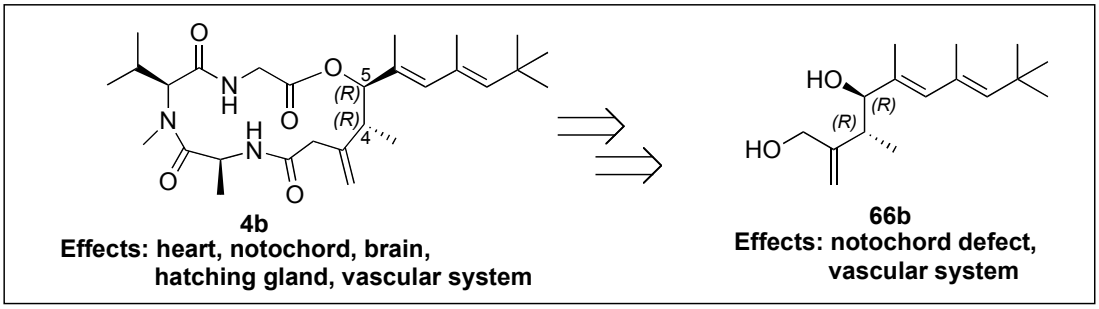
Molecular Structure	Primary effect	All general effect	Pictures
	ISV change	Abnormal development	
	ISV Over-expression	-	
	ISV change	-	
	ISV Over-expression	-	
	ISV change	Abnormal development	

Molecular Structure	Primary effect	All general effect	Pictures
	ISV change	Gross defect and lethal	-
	ISV change	Abnormal blood vessel development	

1.6 Conclusion

In conclusion, the total synthesis of natural (4*R*, 5*R*)-antillatoxin and its analogs has been achieved in 9 steps (from bromide **43** and aldehyde **41** - strategy 2) in 23% overall yield. Our strategy provides practical and easy entry into key intermediates and analogues. Notable features of this synthesis include the indium-mediated allylation of a secondary allylic bromide with aldehyde in aqueous media, and an oxidation-reduction sequence to control the two chiral centres at C_4 and C_5. Especially noteworthy is the convergent nature of this synthetic strategy and the incorporation of all the necessary functionalities in the early stages of the synthesis. The procedure developed here can be used for large scale synthesis of other biological interesting natural products.

Screening of this library of simpler fragments obtained during the process of the total synthesis compounds has resulted in the discovery of other potent compounds. This simple screen utilizing zebrafish embryos has resulted in the discovery of bioactive fragments (4*R*, 5*R*)-**66b** which display similar activity as (4*R*, 5*R*)-antillatoxin. These interesting results provide further evidence on the ease and usefulness of zebrafish embryos as a simple tool for fast biological evaluation in drug discovery research.



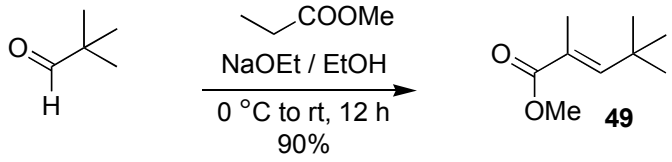
Scheme 1-23

1.7 Experimental

THF was distilled from sodium/benzophenone. Hexane and dichloromethane were distilled from CaH_2. TLC was carried out with pre-coated Merck 60 F_{254} plates. Silica gel 60 (Merck, 400-630 mesh) was used for column chromatography. Infrared spectra were recorded on a Bio-Rad FTS 165 FTIR spectrometer. Liquid samples were examined as film between NaCl salt plates. ^{1}H and ^{13}C NMR spectra were taken in $CDCl_3$ on Bruker DPX300 and Bruker AMX500 and referenced to internal tetramethylsilane ($SiMe_4$). Chemical shifts for ^{1}H NMR spectra are reported as δ in units of parts per million (ppm) downfield from $SiMe_4$ (δ 0.0) and relative to the signal of chloroform-d (δ 7.2600, singlet). Multiplicities were given as: s (singlet); brs (broad singlet); d (doublet); t (triplet); q (quartet); dd (doublets of doublet); dt (doublets of triplet); dtq (doublets of triplets of quartet); or m (multiplets). The number of protons (n) for a given resonance is indicated by nH. Coupling constants are reported as a *J* value in Hz. Carbon nuclear magnetic resonance spectra (^{13}C NMR) are reported as δ in units of parts per million (ppm) downfield from $SiMe_4$ (δ 0.0) and relative to the signal of chloroform-d (δ 77, triplet).

Mass spectral analyses were carried out on a VG 7035 micromass mass spectrophotometer at a source temperature of 200 ºC and at an ion current of 70 eV. Mass spectral data were reported in units of mass to charge (m/z) and % intensity.

(*E*)-methyl 2,4,4-trimethylpent-2-enoate (49)



To a mixture of methyl propionate (24.1 mL, 0.25 mol) and sodium sand (1.45 g, 0.063 mol) at 0 °C was added catalytic amount of absolute ethanol (0.4 mL). trimethylacetaldehyde (4.3 g, 5.43 mL, 50 mmol) was added dropwise. The reaction mixture was stirred at 0 °C to room temperature for 12h. After the reaction was completed, the reaction mixture was poured into saturated NH_4Cl and extracted with ether (x3). The combined organic extracts washed with brine, dried over $MgSO_4$ and concentrated. The residue was purified by flash chromatography on silica gel, elution with hexane/ethyl acetate, 20:1, to afford the pure **49** as a yellowish oil, 7.78 g (90%).

$\mathbf{R}_f$ 0.78 (hexane/ethyl acetate, 4:1);

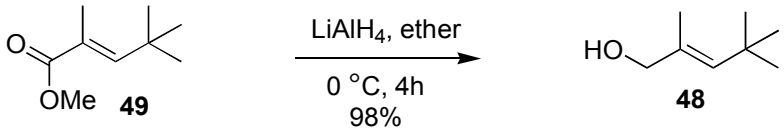
^{1}H NMR (300 MHz, $CDCl_3$): δ 1.18 (9H, s, -C(C**H**$_3$)$_3$), 1.95 (3H, d, *J* = 1.4 Hz, -C-C**H**$_3$), 3.72 (3H, s, -OC**H**$_3$), 6.80 (1H, q, *J* = 1.4 Hz, -C**H**=C-) ppm;

^{13}C NMR (75 MHz, $CDCl_3$): δ 13.3 (-CH=C-**C**H$_3$), 30.1 (-**C**(CH$_3$)$_3$), 33.0 (-C(**C**H$_3$)$_3$), 51.8 (-O**Me**), 126.4 (-CH=**C**-), 151.5 (-**C**H=C-), 169.8 (-**C**O$_2$Me) ppm;

IR (neat, cm^{-1}): 2959, 2870, 1716, 1639, 1466, 1436, 1365, 1284, 1251;

HRMS (EI) m/z (M^+): obsd 156.1157, calcd 156.1150 for $C_9H_{16}O_2$.

(*E*)-2,4,4-trimethylpent-2-en-1-ol (48)



To a mixture of $LiAlH_4$ (0.4 g, 10.5 mmol) in anhydrous ether (20 mL) at 0 °C was added **49** (1.56 g, 10 mmol) in ether (10 mL) dropwise. The reaction mixture was

stirred at 0 °C and the reaction progress was monitored by TLC. After completion, the reaction mixture was quenched with saturated Na_2SO_4 at 0 °C until white precipitate was deposited. The mixture was filtered, washed with ether and dried over $MgSO_4$ and concentrated in *vacuo*. The residue was purified by flash chromatography on silica gel, eluting with hexane/ethyl acetate, 10:1) to afforded **48** as a colorless oil, 1.28 g (98%).

R_f 0.47 (hexane/ethyl acetate, 4:1);

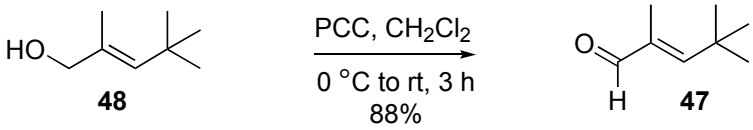
^{1}H NMR (300 MHz, $CDCl_3$): δ 1.12 (9H, s, -C(C**H**$_3$)$_3$), 1.78 (3H, d, *J* = 1.2 Hz, -C-C**H**$_3$), 3.92 (2H, s, -C**H**$_2$-OH), 5.42 (1H, q, *J* = 1.2 Hz, -C**H**=C-) ppm;

^{13}C NMR (75 MHz, $CDCl_3$): δ 14.7 (-CH=C-**C**H$_3$), 30.9 (-**C**(CH$_3$)$_3$), 32.2 (-C(**C**H$_3$)$_3$), 70.8 (-**C**H$_2$OH), 133.3 (-CH=**C**-), 136.6 (-**C**H=C-) ppm;

IR (neat cm^{-1}): 3331, 2957, 2867, 1657, 1465, 1363;

HRMS (EI) m/z (M^+): obsd 128.1196, calcd 128.1201 for $C_8H_{13}O$.

(*E*)-2,4,4-trimethylpent-2-enal (47)



To a mixture of PCC (6.47 g, 30 mmol), 4Å molecular sieve powder (3 g) and silica gel (3 g) in anhydrous CH_2Cl_2 (30 mL) at 0 °C was added **48** (1.28 g, 10.1 mmol) prediluted in anhydrous CH_2Cl_2 (5 mL). The reaction mixture was stirred for 3h. After completion (monitored by TLC), the reaction mixture was filtered through silica gel to afford the product **47** as a yellowish oil, 1.1 g (88%).

R_f 0.75 (hexane/ethyl acetate, 4:1);

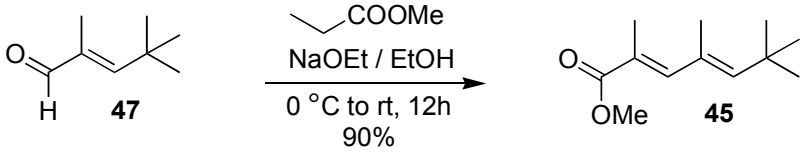
^{1}H NMR (300 MHz, $CDCl_3$): δ 1.24 (9H, s, -C(C**H**$_3$)$_3$), 1.86 (3H, d, *J* = 1.3 Hz, -C-C**H**$_3$), 6.40 (1H, d, *J* = 1.3 Hz, -C**H**=C-), 9.30 (1H, s, -C**H**O) ppm;

^{13}C NMR (75 MHz, $CDCl_3$): δ 9.8 (-CH=C-**C**H_3), 29.7 (-**C**$(CH_3)_3$), 34.2 (-C(**C**$H_3)_3$), 123.8 (-CH=**C**-), 138.5 (-**C**H=C-), 196.8 (-**C**HO) ppm;

IR (neat, cm^{-1}): 2961, 2869, 1691, 1643, 1467, 1366, 1231;

HRMS (EI) m/z (M^+): obsd 126.1020, calcd 126.1044 for $C_8H_{14}O$.

(2*E*,4*E*)-methyl 2,4,6,6-tetramethylhepta-2,4-dienoate (45)



To a mixture of methyl propionate (72.3 mL, 0.25 mol) and sodium sand (0.9 g, 39 mmol) at 0 °C was added catalytic amount of absolute ethanol (0.3 mL). Consequently **47** (3.84 g, 30 mmol) was added dropwise. The reaction mixture was stirred for 12h. After completion the reaction mixture was poured into sat. NH_4Cl at 0 °C and extracted with ether. The combined etherates was washed with brine, dried over anhydrous $MgSO_4$ and concentrated in *vacuo*. The residue was purified by flash chromatography on silica gel to afford **45** as a yellowish oil, 5.3 g (90%).

R_f 0.78 (hexane/ethyl acetate, 4:1);

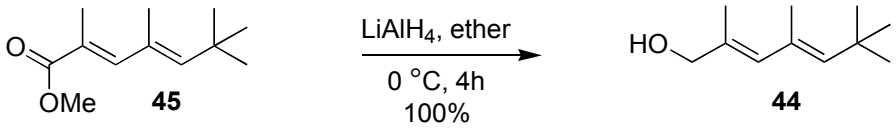
^{1}H NMR (300 MHz, $CDCl_3$): δ 1.16 (9H, s, -C(C**H**$_3)_3$), 1.91 (3H, d, *J* = 1.3 Hz, -CH=C-C**H**$_3$), 1.97 (3H, d, *J* = 1.3 Hz, -CH=C-C**H**$_3$), 3.74 (3H, s, -COOC**H**$_3$), 5.56 (1H, s, -C**H**=C-), 7.08 (1H, s, -C**H**=C-) ppm;

^{13}C NMR (75 MHz, $CDCl_3$): δ 13.9 (-CH=C-**C**H_3), 17.3 (-CH=C-**C**H_3), 30.7 (-**C**$(CH_3)_3$), 33.0 (-C(**C**$H_3)_3$), 51.8 (-O**Me**), 124.9 (-CH=**C**-), 130.8 (-CH=**C**-), 145.3 (-**C**H=C-), 145.5 (-**C**H=C-), 169.7 (-**C**O_2Me) ppm;

IR (neat, cm^{-1}): 2956, 2888, 1713, 1625, 1465, 1435, 1386, 1363;

HRMS (EI) m/z (M^+): obsd 196.1457, calcd 196.1463 for $C_{12}H_{20}O_2$.

(2*E*,4*E*)-2,4,6,6-tetramethylhepta-2,4-dien-1-ol (44)



To a mixture of $LiAlH_4$ (0.8 g, 21 mmol) in anhydrous ether (30 mL) at 0 °C was added **45** (2.52 g, 12 mmol) in ether (30 mL) dropwise. The reaction mixture was stirred at 0 °C and the reaction progress was monitored by TLC. After completion, the reaction mixture was quenched with saturated Na_2SO_4 at 0 °C until white precipitate was deposited. The mixture was filtered, washed with ether and dried over $MgSO_4$ and concentrated in *vacuo*. The residue was purified by flash chromatography on silica gel, eluting with hexane/ethyl acetate, 10:1) to afforded **44** as a colorless oil, 2.02 g (100%).

R_f 0.44 (hexane/ethyl acetate, 4:1);

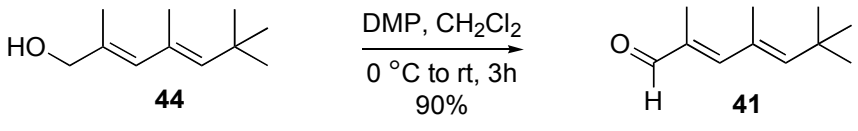
^{1}H NMR (300 MHz, $CDCl_3$): δ 1.15 (9H, s, -C(C**H**$_3$)$_3$), 1.79 (3H, d, *J* = 1.35 Hz, -C-C**H**$_3$), 1.83 (3H, d, *J* = 1.35 Hz, -C-C**H**$_3$), 4.03 (2H, s, -C**H**$_2$-OH), 5.33 (1H, brs, -C**H**=C-), 5.85 (1H, brs, -C**H**=C-) ppm;

^{13}C NMR (75 MHz, $CDCl_3$): δ 15.2 (-CH=C-**C**H$_3$), 17.9 (-CH=C-**C**H$_3$), 31.0 (-**C**(CH$_3$)$_3$), 32.6 (-C(**C**H$_3$)$_3$), 69.5 (-**C**H$_2$OH), 130.9 (-CH=**C**-), 131.5 (-CH=**C**-), 133.8 (-**C**H=C-), 140.6 (-**C**H=C-) ppm;

IR (neat cm^{-1}): 3332, 2956, 1645, 1465, 1362;

HRMS (EI) m/z (M^+): obsd 168.1516, calcd 168.1514 for $C_{11}H_{20}O$.

(2*E*,4*E*)-2,4,6,6-tetramethylhepta-2,4-dienal (41)



To a solution of Dess-Martin reagent (8.66 g, 20.4 mmol) in anhydrous CH_2Cl_2 (40 mL) was added dropwise **44** (2.86 g, 17 mmol) prediluted in CH_2Cl_2 (20 mL) at 0 °C. The reaction mixture was stirred under nitrogen at 0 °C for 3h. After completion, the reaction mixture was diluted with ether and poured slowly into a $Na_2S_2O_3$: $NaHCO_3$ (1:1) solution and stirred for 10 minutes and extracted with ether. The combine etherate layer was washed with $NaHCO_3$, brine and dried over anhydrous $MgSO_4$. Solvent was removed by concentration in *vacuo*. The residue was purified by flash chromatography on silica gel to provide **41** as a yellowish oil, 2.54 g (90%).

$\mathbf{R}_f$ 0.78 (hexane/ethyl acetate, 4:1);

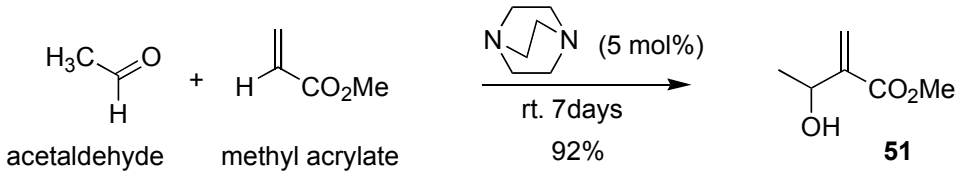
^{1}H NMR (300 MHz, $CDCl_3$): δ 1.20 (9H, s, -C(C**H**$_3$)$_3$), 1.93 (3H, d, *J* = 1.3 Hz, -C-C**H**$_3$), 2.05 (3H, d, *J* = 1.3 Hz, -C-C**H**$_3$), 5.85 (1H, brs, -C**H**=C-), 6.68 (1H, brs, -C**H**=C-), 9.37 (1H, s, -C**H**O) ppm;

^{13}C NMR (75 MHz, $CDCl_3$): δ 10.7 (-CH=C-**C**H$_3$), 17.1 (-CH=C-**C**H$_3$), 30.6 (-**C**(CH$_3$)$_3$), 33.3 (-C(**C**H$_3$)$_3$), 132.0 (-CH=**C**-), 135.4 (-CH=**C**-), 150.2 (-**C**H=C-), 157.3 (-**C**H=C-), 196.3 (-**C**HO) ppm;

IR (neat, cm^{-1}): 2959, 2868, 1727, 1683, 1609, 1466, 1364;

HRMS (EI) m/z (M^+): obsd 166.1368, calcd 166.1358 for $C_{11}H_{18}O$.

Methyl 3-hydroxy-2-methylenebutanoate (51)



To a mixture of methyl acrylate (50 mL, 0.556 mol) and acetaldehyde (47 mL, 0.832 mol) was added 5% mol of DABCO (3.12 g, 0.027 mol). The reaction mixture was stirred at room temperature for 7 days. After completion, CH_2Cl_2 was added and the

mixture was treated with 1M HCl, *sat*. $NaHCO_3$ solution, brine, dried over anhydrous $MgSO_4$ and concentrated in *vacuo*. Purification through flash column chromatography with 10 % ethyl acetate in hexane to afford the product **51** as colorless oil in 92% (66.6 g) of yield.

$\mathbf{R}_f$ 0.31 (hexane/ethyl acetate, 4:1);

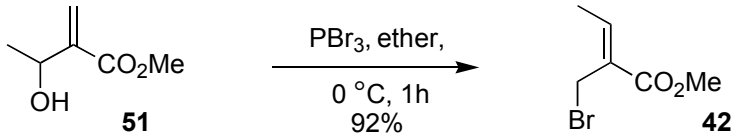
^{1}H NMR (300 MHz, $CDCl_3$): δ 1.38 (3H, d, *J* = 6.5 Hz, -CH-C**H**$_3$), 2.82 (1H, brs, -O**H**), 3.79 (3H, s, -COOC**H**$_3$), 4.61 (1H, q, *J* = 6.5 Hz, -C**H**-OH), 5.84 (1H, d, *J* = 0.55 Hz, -C=C**H**$_2$), 6.22 (1H, d, *J* = 0.55 Hz, -C=C**H**$_2$) ppm;

^{13}C NMR (75 MHz, $CDCl_3$): δ 22.1 (-CH-**C**H$_3$), 51.9 (-CO_2**Me**), 67.1 (-**C**HOH), 124.2 (-C=**C**H$_2$), 143.5 (-**C**=CH$_2$), 167.1 (-**C**O_2Me) ppm;

IR (neat, cm^{-1}): 3426, 2978, 1713, 1630, 1440, 1368;

HRMS (EI) m/z (M^+) : obsd 130.0628, calcd 130.0630 for $C_6H_{10}O_3$.

(*Z*)-methyl 2-(bromomethyl)but-2-enoate (42)



To a solution of **51** (26 g, 0.2 mol) in anhydrous ether (100 mL) at 0 °C was added phosphorus tribromide (19 mL, 0.2 mol) dropwise. The mixture was stirred at 0 °C for 1h. After the reaction completed (monitored by TLC), the mixture was poured into ice water. The solution was extracted with ether and the combined etherate was washed with *sat*. $NaHCO_3$ solution, brine, dried over anhydrous $MgSO_4$ and concentrated in *vacuo*. The residue was purified by flash chromatography to afford **42** as a colorless oil, 35.4 g (92%).

$\mathbf{R}_f$ 0.70 (hexane/ethyl acetate, 4:1);

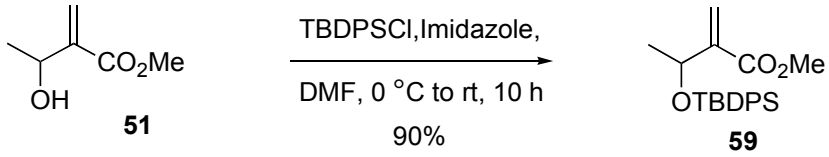
^{1}H NMR (300 MHz, $CDCl_3$): δ 1.92 (3H, d, *J* = 7.25 Hz, -CH-C**H**$_3$), 3.80 (3H, s, -COOC**H**$_3$), 4.24 (2H, s, -C**H**$_2$-Br), 7.06 (1H, q, *J* = 7.25 Hz, -C**H**=C-) ppm;

^{13}C NMR (75 MHz, $CDCl_3$): δ 14.5 (-CH-**C**H_3), 24.0 (-**C**H_2Br), 52.1 (-CO_2**Me**), 130.3 (-C=**C**H-), 143.4 (-**C**=CH-), 166.0 (-**C**O_2Me) ppm;

IR (neat, cm^{-1}): 2991, 2952, 1716, 1645, 1382;

HRMS (EI) m/z (M^+): obsd 191.9814, calcd 191.9786 for $C_6H_9{}^{79}BrO_2$.

Methyl 3-(*tert*-butyldiphenylsilyloxy)-2-methylenebutanoate (59)



To a stirred solution of **51** (1.07 g, 8.25 mmol) in anhydrous DMF (20 mL) was added in imidazole (0.9 g, 13 mmol) followed by tert-butyldiphenylsilyl chloride (2.5 mL, 9.5 mmol) at 0 °C under nitrogen. The reaction mixture was stirred for 10h at room temperature. After completion, the reaction mixture was poured into H_2O and extracted with ethyl acetate. The combined organic extracted were washed with brine, dried over anhydrous $MgSO_4$ and concentrated in *vacuo*. The residue was purified by flash chromatography on silica gel, eluting with hexane-ethyl acetate (20:1) to afforded **59** as a colorless oil, 2.73 g (90%).

R$_f$ 0.69 (hexane/ethyl acetate, 4:1);

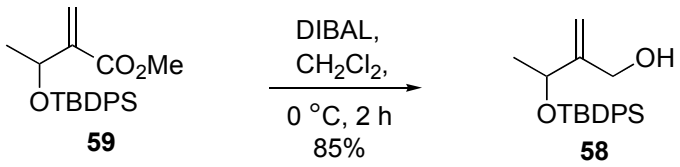
^{1}H NMR (300 MHz, $CDCl_3$): δ 1.09 (9H, s, -C(C**H**$_3$)$_3$), 1.18 (3H, d, *J* = 6.24 Hz, -CH-C**H**$_3$), 3.70 (3H, s, -CO_2**Me**), 4.74 (1H, q, *J* = 6.24 Hz, -C**H**-CH_3), 6.11 (1H, t, *J* = 1.38 Hz, -C=C**H**$_2$), 6.24 (1H, t, *J* = 1.05 Hz, -C=C**H**$_2$), 7.34-7.43 (6H, m, -Ph-**H**), 7.59-7.70 (4H, m, -Ph-**H**) ppm;

^{13}C NMR (75 MHz, $CDCl_3$): δ 19.3 (-**C**$(CH_3)_3$), 24.5 (-CH**C**H_3), 27.0 (-C(**C**$H_3)_3$), 51.6 (-O**Me**), 67.8 (-**C**H-OTBDPS), 123.9 (-C=**C**H_2), 127.6, (Ph-**C** x4), 129.7 (Ph-**C** x2), 134.1 (Ph-**C***q* x2), 135.9 (Ph-**C** x4), 145.1 (-**C**=CH_2), 166.5 (-**C**O_2Me) ppm;

IR (neat, cm^{-1}): 3076, 2962, 2941, 1729, 1430;

HRMS (EI) m/z [(M-C_4H_9)$^+$]: obsd 311.1102, calcd 311.1103 for $C_{18}H_{19}O_3Si$.

Methyl 3-(*tert*-butyldiphenylsilyloxy)-2-methylenebutanoate (58)



To a solution of **59** (9.20 g, 25 mmol) in anhydrous CH_2Cl_2 (150 mL) was added dropwise 1.0 M solution of DIBAL-H (50 mL, 50 mmol) at 0 °C under N_2. The reaction progress was monitored by TLC. After completion, saturated Na_2SO_4 solution was added dropwise until white precipitate was deposited and the mixture was stirred for another 10 minutes at room temperature. The resulting slurry precipitate was filtered and washed with ether. The combined organic layers was dried over anhydrous $MgSO_4$, filtered and concentrated in *vacuo*. The residue was purified by flash chromatogaraphy on silica gel, eluting with hexane-ethyl acetate (10:1) to afford **58** as a colorless oil, 7.21 g (85%).

R$_f$ 0.56 (hexane/ethyl acetate, 4:1)

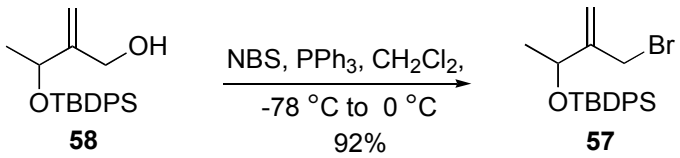
^{1}H NMR (300 MHz, $CDCl_3$): δ 1.07 (9H, s, -C(C**H**$_3)_3$), 1.19 (3H, d, *J* = 6.6 Hz, -CH-C**H**$_3$), 4.11 (1H, dd, *J* = 13.41, 6.96 Hz, -C**H**$_2$-OH), 4.29 (1H, dd, *J* = 13.41, 4.53 Hz, -C**H**$_2$-OH), 4.43 (1H, q, *J* = 6.6 Hz, -C**H**-CH_3), 4.99 (2H, dd, *J* = 1.38, 1.05 Hz, -C=C**H**$_2$), 7.34-7.44 (6H, m, -Ph-**H**), 7.64-7.71 (4H, m, -Ph-H) ppm;

^{13}C NMR (75 MHz, $CDCl_3$): δ 19.2 (-**C**$(CH_3)_3$), 23.6 (-CH**C**H_3), 27.0 (-C(**C**$H_3)_3$), 63.3 (-**C**H_2OH), 72.2 (-**C**H-OTBDPS), 110.5 (-C=**C**H_2), 127.6 (Ph-**C** x4), 129.7 (Ph-**C** x2), 133.5(Ph-**C***q*), 134.0 (Ph-**C***q*), 135.9 (Ph-**C** x4), 151.3 (-**C**=CH_2) ppm;

IR (neat, cm^{-1}): 3386, 3073, 3052, 2961, 2932, 1473, 1428;

HRMS (EI) m/z [(M-C_4H_9)$^+$]: obsd 283.1154, calcd 283.1154 for $C_{17}H_{19}O_2Si$.

(3-(bromomethyl)but-3-en-2-yloxy)(*tert*-butyl)diphenylsilane (57)



To a solution of **58** (6.8 g, 20 mmol) in anhydrous CH_2Cl_2 (100 mL) at 0 °C was added PPh_3 (6.4 g, 24 mmol) in one portion. The reaction mixture was stirred at 0 °C for 10 minutes. After all of the PPh_3 has dissolved, NBS (4 g, 22 mmol) was added in one portion at -78 °C. The resulting solution was stirred at -78 °C for 30 minutes then transfer to an ice bath at 0 °C. The reaction progress was monitored by TLC. After completion, ether and H_2O were added subsequently. The mixture was partitioned, and the organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated in *vacuo*. The residue was purified by flash chromatography on silica gel, eluting with hexane-ethyl acetate (40:1) to afford **57** as a colorless oil, 7.4 g (92%).

R_f 0.90 (hexane/ethyl acetate, 4:1);

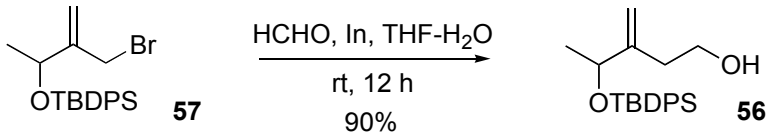
^{1}H NMR (300 MHz, $CDCl_3$): δ 1.08 (9H, s, -C(C**H**$_3)_3$), 1.21 (3H, d, *J* = 6.42 Hz, -CH-C**H**$_3$), 3.98 (2H, s, -C**H**$_2$-Br), 4.51 (1H, q, *J* = 6.42 Hz, -C**H**-CH_3), 5.24 (1H, s, -C=C**H**$_2$), 5.32 (1H, s, -C=C**H**$_2$), 7.34-7.44 (6H, m, -Ph-**H**), 7.64-7.71 (4H, m, -Ph-**H**) ppm;

^{13}C NMR (75 MHz, $CDCl_3$): δ 19.3 (-**C**$(CH_3)_3$), 23.6 (-CH**C**H_3), 27.0 (-C(**C**$H_3)_3$), 32.2 (-**C**H_2Br), 70.4 (-**C**H-OTBDPS), 115.2 (-C=**C**H_2), 127.6 (Ph-**C** x4), 129.7 (Ph-**C** x2), 133.6 (Ph-**C***q*), 134.3 (Ph-**C***q*), 135.9 (Ph-**C** x4), 148.9 (-**C**=CH_2) ppm;

IR (neat, cm^{-1}): 3075, 3052, 2965, 2932, 2859, 1473, 1428;

HRMS (EI) m/z [(M-C_4H_9)$^+$]: obsd 345.0308, calcd 345.0310 for $C_{17}H_{18}BrOSi$.

4-(*tert*-butyldiphenylsilyloxy)-3-methylenepentan-1-ol (56)



To a mixture of **57** (6.0 g, 14.8 mmol) and formaldehyde solution (35%-40% in water) (40 mL) in THF (40 mL) were added indium (3.41 g, 29.6 mmol). The mixture was stirred vigorously at room temperature for 12h, after which the reaction mixture was extracted with ethyl acetate. The organic extracts were washed with H_2O, brine, dried over anhydrous Na_2SO_4 and concentrated in *vacuo*. The crude product was purified by flash chromatography on silica gel, eluting with hexane-ethyl acetate (10:1) to afforded **56** as colorless oil, 4.74 g (90%).

R$_f$ 0.39 (hexane/ethyl acetate, 4:1);

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.07 (9H, s, -C(C**H**$_3)_3$), 1.15 (3H, d, *J* = 6.44 Hz, -CH-C**H**$_3$), 2.24 (1H, dt, *J* = 14.81, 5.55 Hz, -C**H**$_2$CH$_2$OH), 2.39 (1H, dt, *J* = 14.81, 6.63 Hz, -C**H**$_2$CH$_2$OH), 3.58-3.74 (2H, m, -C**H**$_2$-OH), 4.27 (1H, q, *J* = 6.44 Hz, , -C**H**-CH$_3$), 4.81 (1H, s, C=C**H**$_2$), 5.03 (1H, s, -C=C**H**$_2$), 7.34-7.45 (6H, m, -Ph-**H**), 7.64-7.70 (4H, m, -Ph-**H**) ppm;

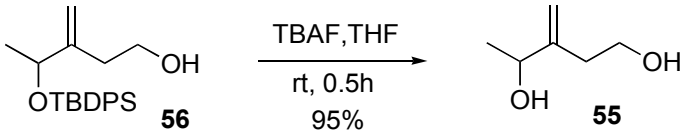
^{13}C NMR (75 MHz, $CDCl_3$): δ 19.2 (-**C**$(CH_3)_3$), 23.2 (-CH**C**H_3), 27.0 (-C(**C**$H_3)_3$), 34.8 (-**C**H_2CH$_2$OH), 61.5 (-**C**H_2OH), 73.0 (-**C**H-OTBDPS), 111.9 (-C=**C**H_2), 127.6

(Ph-**C** x4), 129.7 (Ph-**C** x2), 133.7 (Ph-**C***q*), 134.1 (Ph-**C***q*), 135.9 (Ph-**C** x4), 149.3 (-**C**=CH_2) ppm;

IR (neat, cm^{-1}): 3441, 3369, 3075, 3052, 2965, 2931, 2858, 1473, 1428;

HRMS (EI) m/z [(M-C_4H_9)$^+$]: obsd 297.1316, calcd 297.1311 for $C_{18}H_{21}O_2Si$.

3-methylenepentane-1,4-diol (55)



To a solution of **56** (1.0 g, 2.8 mmol) in THF (6 mL) was treated with TBAF (4.2 mL, 1.0 M in THF solution, 4.2 mmol) at room temperature. The mixture was stirred for 30 minutes. After the reaction was completed (monitor by TLC), THF was removed in *vacuo*. The residue was purified by flash chromatography on silica gel, eluting with hexane-ethyl acetate (2:1 to 1:1). The diol **55** was obtained as a colorless oil, 0.30 g (95%).

R$_f$ 0.12 (hexane/ethyl acetate, 1:1);

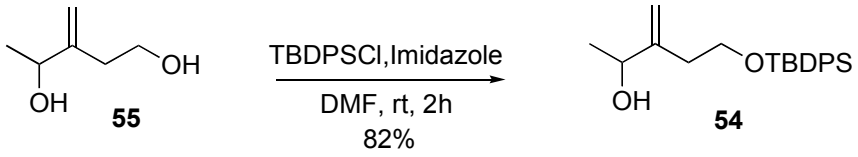
^{1}H NMR (300 MHz, $CDCl_3$): δ 1.30 (3H, d, *J* = 6.27 Hz, -CH-C**H**$_3$), 2.29 (1H, dt, *J* = 14.21, 5.22 Hz, -C**H**$_2$$CH_2OH$), 2.42 (1H, dt, *J* = 14.21, 6.09 Hz, -C**H**$_2$$CH_2OH$), 3.66-3.82 (2H, m, -C**H**$_2$-OH), 4.30 (1H, q, *J* = 6.27 Hz, -C**H**-CH_3), 4.90 (1H, s, -C=C**H**$_2$), 5.10 (1H, s, -C=C**H**$_2$) ppm;

^{13}C NMR (75 MHz, $CDCl_3$): δ 22.0 (-CH-**C**H_3), 35.0 (-**C**H_2CH_2OH), 62.3 (-**C**H_2OH), 70.9 (-**C**H-OH), 112.2 (-C=**C**H_2), 150.1 (-**C**=CH_2) ppm;

IR (neat, cm^{-1}): 3386, 2976, 2936, 2887;

HRMS (EI) m/z [(M-H_2O)$^+$]: obsd 98.0733, calcd 98.0732 for $C_6H_{10}O$.

5-(*tert*-butyldiphenylsilyloxy)-3-methylenepentan-2-ol (54)



To a solution of **55** (0.60 g, 5 mmol) in anhydrous DMF (30 mL) at 0 °C was added imidazole (0.70 g, 10 mmol) in one portion. After the imidazole has dissolved, *tert*-butyldiphenylsilyl chloride (1.5 mL, 5.75 mmol) was added in. After the reaction was completed (monitor by TLC), the reaction mixture was poured into ice water and extracted with ethyl acetate. The combined organic extract was washed with brine, dried over anhydrous $MgSO_4$ and concentrated in *vacuo*. The residue was purified by flash chromatography on silica gel to afford **54** as a colorless oil, 1.45 g (82%).

R_f 0.66 (hexane/ethyl acetate, 4:1);

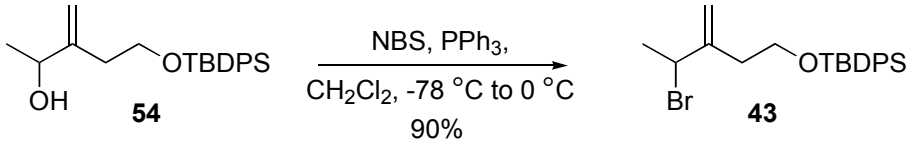
^{1}H NMR (300 MHz, $CDCl_3$): δ 1.05 (9H, s, -C(C**H**$_3$)$_3$), 1.27 (3H, d, *J* = 6.45 Hz, -CH-C**H**$_3$), 2.27 (1H, dt, *J* = 14.26, 5.58 Hz, -C**H**$_2$CH$_2$OTBDPS), 2.45 (1H, dt, *J* = 14.26, 6.63 Hz, -C**H**$_2$CH$_2$OTBDPS), 3.73-3.83 (2H, m, -C**H**$_2$OTBDPS), 4.27 (1H, q, *J* = 6.45 Hz, -C**H**-OH), 4.83 (1H, s, -C=C**H**$_2$), 5.07 (1H, s, -C=C**H**$_2$), 7.36-7.46 (6H, m, -Ph-**H**), 7.66-7.71 (4H, m, -Ph-**H**) ppm;

^{13}C NMR (75 MHz, $CDCl_3$): δ 19.1 (-**C**(CH$_3$)$_3$), 22.3 (-CH**C**H$_3$), 26.8 (-C(**C**H$_3$)$_3$), 34.7 (-**C**H$_2$CH$_2$OTBDPS), 63.1 (-**C**H$_2$OTBDPS), 70.8 (-**C**HOH), 111.2 (-C=**C**H$_2$), 127.7 (Ph-**C** x4), 129.8 (Ph-**C** x2), 133.4 (Ph-**C***q*), 134.8 (Ph-**C***q*), 135.6 (Ph-**C** x4), 150.6 (-**C**=CH$_2$) ppm;

IR (neat, cm^{-1}): 3398, 3072, 3053, 2960, 2931, 2858, 1472, 1458;

HRMS (EI) m/z [(M-C$_4$H$_9$)$^+$]: obsd 297.1324, calcd 297.1311 for $C_{18}H_{21}O_2Si$.

(4-bromo-3-methylenepentyloxy)(*tert*-butyl)diphenylsilane (43)



To a solution of **54** (1.05 g, 3 mmol) in anhydrous CH_2Cl_2 (9 mL) at 0 °C was added PPh_3 (0.96 g, 3.6 mmol) in one portion. The reaction mixture was stirred at 0 °C for 10 minutes. After all PPh_3 has dissolved, NBS (0.6 g, 3.3 mmol) was added in one portion at -78 °C. The resulting solution was stirred at -78 °C for 30 minutes then transferred to ice bath at 0 °C. After completion (monitored by TLC), ether and H_2O were added subsequently. The mixture was partitioned, and the organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated in *vacuo*. The residue was purified by flash chromatography on silica gel, eluting with hexane-ethyl acetate (40:1) to afford **43** as a colorless oil, 1.12 g (90%).

R_f 0.85 (hexane/ethyl acetate, 4:1);

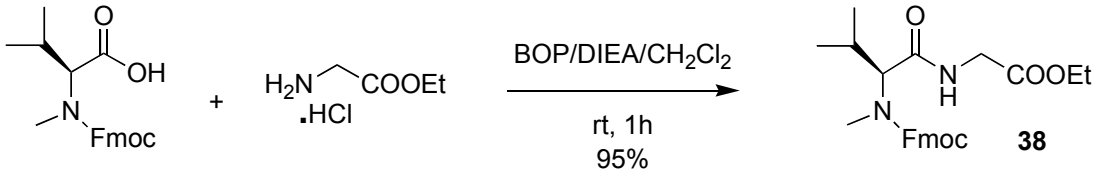
^{1}H NMR (300 MHz, $CDCl_3$): δ 1.07 (9H, s, -C(C**H**$_3$)$_3$), 1.77 (3H, d, *J* = 6.9 Hz, -CH-C**H**$_3$), 2.40-2.60 (2H, m, -C**H**$_2$-C=), 3.84 (2H, t, *J* = 6.6 Hz, -C**H**$_2$-O-), 4.69 (1H, q, *J* = 6.9 Hz, -C**H**-CH$_3$), 4.95 (1H, s, C=C**H**$_2$), 5.21 (1H, s, -C=C**H**$_2$), 7.37-7.46 (6H, m, -Ph-**H**), 7.67-7.70 (4H, m, -Ph-**H**) ppm;

^{13}C NMR (75 MHz, $CDCl_3$): δ 19.2 (-**C**(CH$_3$)$_3$), 24.2 (-CH**C**H$_3$), 26.9 (-C(**C**H$_3$)$_3$), 35.7 (-**C**H$_2$CH$_2$OTBDPS), 52.5 (-**C**HBr), 63.1 (-**C**H$_2$OTBDPS), 113.3 (-C=**C**H$_2$), 127.7 (Ph-**C** x4), 129.7 (Ph-**C** x2), 133.7 (Ph-**C***q*), 133.8 (Ph-**C***q*), 135.6 (Ph-**C** x4), 147.5 (-**C**=CH$_2$) ppm;

IR (neat, cm^{-1}): 3072, 2958, 2931, 2858, 1590, 1428;

HRMS (EI) m/z [(M-C$_4$H$_9$)$^+$]: obsd 359.0469, calcd 359.0467 for $C_{18}H_{20}SiBrO$.

Dipeptide Fmoc-(*S*)-Me-Val-Gly-OEt (38)



To a mixture of N-methyl Fmoc protected L-valine (1 g, 2.8 mmol), glycine ethyl ester hydochloride salt (0.43 g, 3.1 mmol) in CH_2Cl_2 (5 mL) was added benzotriazol-1-yloxytris(dimethylamino)phophonium hexafluorophosphate (BOP) (1.25 g, 2.8 mmol). After the BOP had dissolved, diisopropylethylamine (DIEA) (1.5 mL) was added dropwise. The mixture was stirred at room temperature for 1h. After the reaction was completed (monitor by TLC), the reaction mixture was concentrated in *vacuo*. The residue was purified by flash chromatography on silica gel, eluting with hexane/ethyl acetate (4:1 to 2:1) to afford the dipeptide **38** as a colorless oil, 1.17 g (95%).

$\mathbf{R}_f$ 0.68 (hexane/ethyl acetate, 1:1);

$[\alpha]^{28}_D$ = -88.1° (*c* = 1.0, MeOH);

^{1}H NMR (300 MHz, $CDCl_3$): δ 0.84 (3H, d, *J* = 6.4 Hz, Val-C**H**$_3$), 0.96 (3H, d, *J* = 6.4 Hz, Val-C**H**$_3$), 1.25 (3H, t, *J* = 7.0 Hz, -CH_2-C**H**$_3$), 2.19-2,42 (1H, m, -C**H**-$(CH_3)_2$), 2.89 (3H, s, -N-C**H**$_3$), 3.51 (1H, m, -N**H**-CH_2-), 3.96 (1H, m, -N**H**-CH_2-), 4.12 (2H, q, *J* = 7.0 Hz, -OC**H**$_2$-CH_3), 4.22 (1H, d, *J* = 7.0 Hz, -N-C**H**-), 4.44 (1H, t, *J* = 7.0 Hz, -C**H**-CH_2-O-), 4.68-4.76 (2H, m, -O-C**H**$_2$-CH-), 6.57 (1H, brs, -N**H**), 7.30-7.43 (4H, m, -Ph-**H**), 7.55-7.63 (2H, m, -Ph-**H**), 7.73-7.81 (2H, m, -Ph-**H**) ppm;

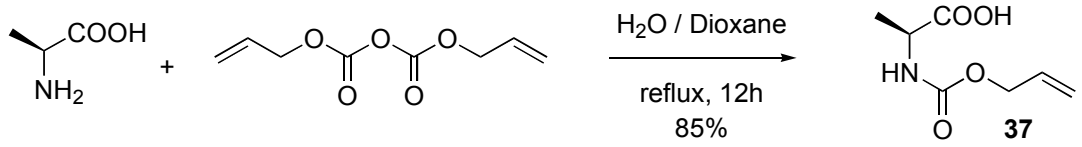
^{13}C NMR (75 MHz, $CDCl_3$): δ 14.1 (-OCH_2**C**H_3), 18.5 (-**C**H_3), 19.4 (-**C**H_3), 26.1 (-**C**$H(CH_3)_2$), 29.7 (-N-**C**H_3), 41.0 (-**C**H-Ph), 47.2 (-NH-**C**H_2-), 61.9 (-O**C**H_2CH_3), 64.6 (-N-**C**H-), 67.6 (-O-**C**H_2-), 119.9 (-Ph-**C**), 124.9 (-Ph-**C**), 126.9 (-Ph-**C**), 127.6 (-Ph-

C), 141.2 (-Ph-**C**), 143.8 (-Ph-**C**), 157.3 (-**C**=O), 169.3 (-**C**=O), 170.5 (-**C**ONH-) ppm;

IR (neat, cm^{-1}): 3342, 3060, 2955, 2872, 1746, 1737, 1708, 1696, 1666, 1537, 1519;

HRMS (EI) m/z (M^{+}): obsd 438.2158, calcd 438.2155 for $C_{25}H_{30}N_2O_5$.

Protection of L-alanine with Alloc (37)



L-alanine (0.40 g, 4.5 mmol), diallydicarbonate (1 g, 5.4 mmol) was dissolved in dioxane (5 mL) and water (5 mL). The mixture was refluxed for 12h under nitrogen. After the reaction was completed (monitored by TLC), the reaction mixture was cooled to room temperature and extracted with ether. The combined ether phase was washed with saturated $NaHCO_3$. The combined aqueous layer was acidified with concentrated HCl until pH=1 at 0 °C and extracted with ethyl acetate. The combined ethyl acetate was washed with saturated NH_4Cl and brine until pH=7, dried over anhydrous Na_2SO_4 and concentrated in *vacuo* to afford the Alloc protected alanine as a pale yellow liquid, 0.66 g (85%).

R$_f$ 0.11 (hexane/ethyl acetate, 1:1);

$[\alpha]^{30}_{D}$ = -14.0° (*c* = 3.2, CH_2Cl_2);

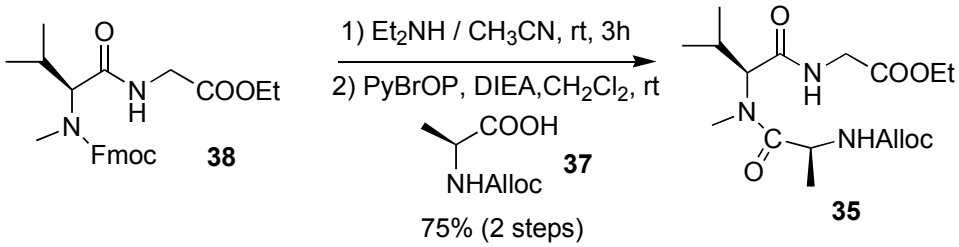
^{1}H NMR (300 MHz, $CDCl_3$): δ 1.47 (3H, d, *J* = 7.2 Hz, -CH-C**H**$_3$), 4.40 (1H, q, *J* = 7.2 Hz, -C**H**-CH$_3$), 4.57-4.65 (2H, m, -O-C**H**$_2$-), 5.21-5.34 (3H, m, -CH=C**H**$_2$, -N**H**), 5.84-5.97 (1H, m, -C**H**=CH$_2$), 6.53 (1H, brs, -COO**H**) ppm;

^{13}C NMR (75 MHz, $CDCl_3$): δ 18.1 (-CH-**C**H$_3$), 49.3 (-NH-**C**H-), 65.9 (-O-**C**H$_2$-), 117.8 (-CH=**C**H$_2$), 132.3 (-**C**H=CH$_2$), 155.9 (-**C**=O), 176.8 (-**C**OOH) ppm;

IR (neat, cm^{-1}): 3417, 1643, 1546, 1530;

HRMS (EI) m/z (M^+): obsd 173.0681, calcd 173.0688 for $C_7H_{11}NO_4$.

Tripeptide Alloc-(*S*)-Ala-(*S*)-Me-Val-Gly-OEt (35)



38 (1.387 g, 3.16 mmol) was dissolved in CH_3CN (33 mL) and diethylamine (1.65 mL, 15.8 mmol) (5% v/v based on CH_3CN). The mixture was stirred at room temperature for 3h. After the rection was completed (monitor by TLC), the reaction mixture was concentrated in *vacuo* to remove the solvent and the residue was used in the next step without further purification.

To the residue was added CH_2Cl_2 (3.5 mL), *N*-Alloc alanine **37** (0.49 g, 2.84 mmol) and bromotripyrrolidino phosphonium hexafluorophosphate (PyBrOP) (2.21 g, 4.31 mmol) in one portion. After PyBrOP had dissolved, diisopropylethylamine (DIEA) (1.1 mL, 6.1 mmol) was added dropwise. The mixture was stirred at room temperature for 3h. The reaction progress was monitored by TLC. After completion, the reaction mixture was concentrated in *vacuo*. The residue was purified by flash chromatography on silica gel, eluting with hexane/ethyl acetate (4:1 to 1:1). The tripeptide **35** was obtained as a colorless oil, 0.78 g (75%).

$\mathbf{R}_f$ 0.38 (Hexane/ethyl acetate, 1:1);

$[\alpha]^{28}_D = -58.8°$ ($c = 0.57$, CH_2Cl_2);

^{1}H NMR (300 MHz, $CDCl_3$): δ 0.84 (3H, d, J = 6.6 Hz, Val-C**H**$_3$), 0.98 (3H, d, J = 6.3 Hz, Val-C**H**$_3$), 1.26 (3H, t, J = 7.3 Hz, -CH_2-C**H**$_3$), 1.35 (3H, d, J = 6.6 Hz, Ala-

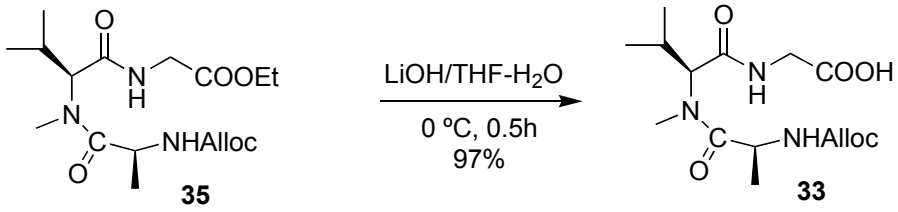
C**H**$_3$), 2.26-2.38 (1H, m, Val-(CH$_3$)$_2$-C**H**-), 3.03 (3H, s, -N-C**H**$_3$), 3.83 (1H, dd, *J* = 17.8, 5.3 Hz, Gly-C**H**$_2$-), 4.08 (1H, dd, *J* = 17.8, 6.6 Hz, Gly-C**H**$_2$-), 4.18 (2H, q, *J* = 7.3 Hz, -C**H**$_2$-CH$_3$), 4.48-4.70 (4H, m, Ala-α-**H**, CH$_2$=CH-C**H**$_2$-, Val-α-**H**), 5.19-5.33 (2H, m, -CH=C**H**$_2$), 5.65 (1H, d, *J* = 7.7 Hz, Ala-N**H**), 5.82-5.97 (1H, m, -C**H**=CH$_2$), 6.55 (1H, brs, Gly-N**H**) ppm;

^{13}C NMR (75 MHz, CDCl$_3$): δ 14.0 (-OCH$_2$**C**H$_3$), 18.4 (-**C**H$_3$), 19.4 (-**C**H$_3$), 25.5 (-**C**H(CH$_3$)$_2$), 30.4 (-N-**C**H$_3$), 40.9 (-NH-**C**H$_2$-), 47.1 (-NH-**C**H-), 61.2 (-O**C**H$_2$CH$_3$), 62.4 (-N-**C**H-), 65.5 (-O**C**H$_2$-), 117.5 (-CH=**C**H$_2$), 132.7 (-**C**H=CH$_2$), 155.4 (-**C**=O), 169.5 (-**C**=O), 170.1 (-N-**C**=O), 174.0 (-N-**C**=O) ppm;

IR (neat, cm^{-1}): 3415, 1722, 1640, 1547;

HRMS (EI) m/z (M$^+$): obsd 371.2081, calcd 371.2056 for $C_{17}H_{29}N_3O_6$.

Tripeptide Alloc-(*S*)-Ala-(*S*)-Me-Val-Gly-OH (33)



To a solution of **35** (0.57 mg, 1.53 mmol) in THF (3 mL) at 0 °C was added a solution of LiOH (229 mg, 5.46 mmol) in water (3 mL). The resulting mixture was stirred at 0 °C for 30 minutes. After dilution with H_2O, the reaction mixture was washed with ether. The aqueous layer was acidified to pH = 3 by the addition of 1M HCl and salted out. The mixture was extracted with ether (x3). The combined organic extract was dried over anhydrous Na_2SO_4, filtered and concentrated to afford the desired product **33** as colorless oil, 0.51 g (97%).

R$_f$ 0.11 (hexane/ethyl acetate, 1:1);

$[\alpha]^{30}_D$ = -112.8° (*c* = 0.37, CH_2Cl_2);

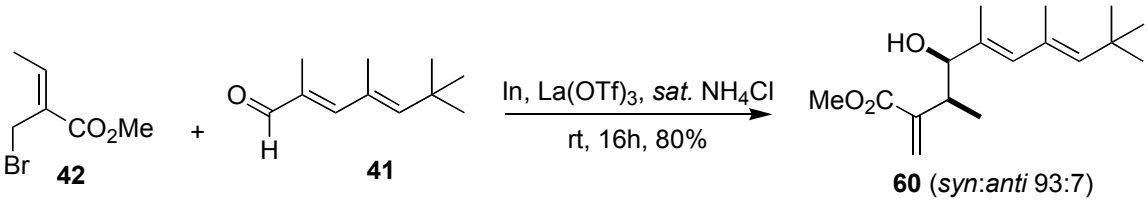
^{1}H NMR (300 MHz, $CDCl_3$): δ 0.82 (3H, d, *J* = 6.4 Hz, Val-C**H**$_3$), 0.95 (3H, d, *J* = 6.4 Hz, Val-C**H**$_3$), 1.29 (3H, d, *J* = 6.8 Hz, Ala-C**H**$_3$), 2.25-2.38 (1H, m, Val-$(CH_3)_2$-C**H**-), 3.03 (3H, s, -N-C**H**$_3$), 3.83-3.94 (1H, m, Val-α-**H**), 4.03-4.19 (1H, m, Ala-α-**H**), 4.53 (2H, d, *J* = 5.2 Hz, CH_2=CH-C**H**$_2$-), 4.62 (2H, d, *J* = 11.2 Hz, Gly-C**H**$_2$-), 4.50-5.20 (1H, brs, COO**H**), 5.17 -5.31(2H, m, C**H**$_2$=CH-CH_2-), 5.78-5.95 (1H, m, -C**H**=CH_2), 6.36 (1H, brs, Ala-N**H**), 6.96 (1H, brs, Gly-N**H**) ppm;

^{13}C NMR (75 MHz, $CDCl_3$): δ 17.9 (-**C**H_3), 18.4 (-**C**H_3), 19.4 (-**C**H_3), 25.6 (-**C**H$(CH_3)_2$), 30.6 (-N-**C**H_3), 40.9 (-NH-**C**H_2-), 47.3 (-NH-**C**H-), 62.8 (-N-**C**H-), 65.7 (-O**C**H_2-), 117.7 (-CH=**C**H_2), 132.6 (-**C**H=CH_2), 155.6 (-**C**=O), 170.0 (-**C**OOH), 172.4 (-N-**C**=O), 174.6 (-N-**C**=O) ppm;

IR (neat, cm^{-1}): 3316, 1712, 1682, 1636, 1588, 1470;

HRMS (EI) m/z (M^+): obsd 343.1742, calcd 343.1744 for $C_{15}H_{25}N_3O_6$.

***Syn*-(5*E*,7*E*)-methyl 4-hydroxy-3,5,7,9,9-pentamethyl-2-methylenedeca-5,7-dienoate (60)**



To a stirred solution of **42** (3.65 mL, 28 mmol) in *sat*. NH_4Cl solution (50 mL) were added indium (2.18 g, 18.9 mmol). After vigorous stirred for 30 minutes at room temperature, La$(OTf)_3$ (5.5 g, 9 mmol) and **41** (1.57 g, 9.46 mmol) were subsequently added. The mixture was stirred vigorously at room temperature for 16h. After the reaction was completed (monitored by TLC), the reaction mixture was extracted with ethyl acetate. The organic extracts were combined and washed with *sat*. $NaHCO_3$ solution, brine, dried over anhydrous Na_2SO_4, and concentrated in *vacuo*. The crude

product was purified by flash chromatography on silica gel, eluting with 5% ethyl acetate in hexane gave **60** as a colorless oil (2.12 g, 80%), the *syn*/*anti* isomer were obtain in the ratio of 93:7.

$\mathbf{R}_f$ 0.47 (hexane/ethyl acetate, 4:1);

***Syn* isomer:**

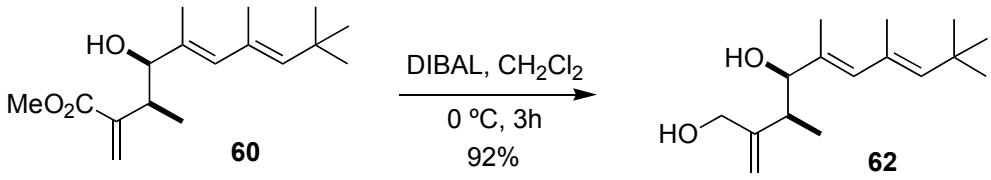
^{1}H NMR (500 MHz, $CDCl_3$): δ 1.11 (3H, d, *J* = 6.95 Hz, -CH-C**H**$_3$), 1.13 (9H, s, -C(C**H**$_3$)$_3$), 1.72 (3H, d, *J* = 1.4 Hz, -C-C**H**$_3$), 1.78 (3H, d, *J* = 0.9 Hz, -C-C**H**$_3$), 2.99 (1H, ddd, *J* = 6.95, 4.15, 0.95 Hz -C**H**-CH$_3$), 3.75 (3H, s, -COOC**H**$_3$), 4.08 (1H, d, *J* = 4.15 Hz, -C**H**-OH), 5.24 (1H, d, *J* = 1.30 Hz, -C=C**H**$_2$), 5.64 (1H, d, *J* = 0.95 Hz, -C=C**H**-), 5.82 (1H, d, *J* = 1.30 Hz, -C=C**H**$_2$), 6.24 (1H, d, *J* = 0.95 Hz, -C=C**H**-) ppm;

^{13}C NMR (125 MHz, $CDCl_3$): δ 13.8 (-**C**H$_3$), 13.8 (-**C**H$_3$), 17.8 (-**C**H$_3$), 30.9 (-C(**C**H$_3$)$_3$), 32.5 (-**C**(CH$_3$)$_3$), 38.9 (-**C**H-CH$_3$), 51.7 (-O**Me**), 78.9 (-**C**HOH), 125.4 (-C=**C**H$_2$), 130.8 (-**C**=CH-), 131.8 (-C=**C**H-), 134.5 (-**C**=CH-), 139.8 (-C=**C**H-), 143.2 (-**C**=CH$_2$), 167.6 (**C**=O) ppm;

IR (neat, cm^{-1}): 3440, 2954, 1717, 1625, 1437;

HRMS (EI) m/z (M^+): obsd 280.2032, calcd 280.2039 for $C_{17}H_{28}O_3$.

***Syn*-(5*E*,7*E*)-3,5,7,9,9-pentamethyl-2-methylenedeca-5,7-diene-1,4-diol (62)**



To a mixture of *syn* **60** (0.7 g, 2.5 mmol) in anhydrous CH_2Cl_2 (5 mL), was added DIBAL-H (5 mL, 5 mmol) at 0 °C and stirred for 3h. After reduction was completed (monitored by TLC), *sat*. Na_2SO_4 solution was added until white precipitate was deposited. The mixture was filtered, dried over anhydrous $MgSO_4$ and concentrated in

vacuo. The residue was purified by flash chromatography on silica gel (hexane ethyl / acetate, 4:1) to afford the pure *syn* **62** as a colorless oil, 0.58 g (92%).

R_f 0.40 (hexane/ethyl acetate, 2:1);

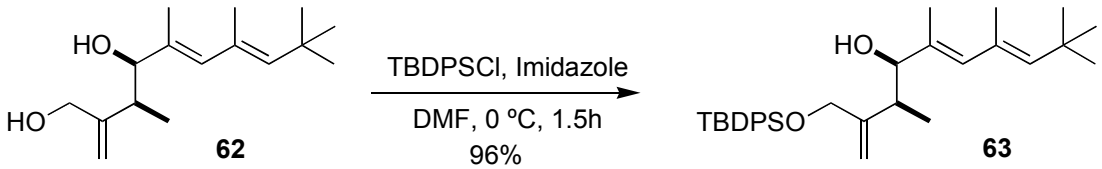
^{1}H NMR (500 MHz, $CDCl_3$): δ 1.02 (3H, d, *J* = 6.96 Hz, -CH-C**H**$_3$), 1.27 (9H, s, -C(C**H**$_3$)$_3$), 1.70 (3H, d, *J* = 1.05 Hz, -C-C**H**$_3$), 1.79 (3H, d, *J* = 1.05 Hz, -C-C**H**$_3$), 2.54 (1H, dq, *J* = 6.96, 3.84 Hz, -C**H**-CH$_3$), 2.63 (2H, brs, -CH$_2$O**H**, -CHO**H**), 4.04 (1H, d, *J* = 3.84 Hz, -C**H**-OH), 4.06 (1H, d, *J* = 13.23 Hz, -C**H**$_2$-OH), 4.14 (1H, d, *J* = 13.23 Hz, -C**H**$_2$-OH), 4.99 (1H, brs, -C=C**H**-), 5.13 (brs, 1H, -C=C**H**$_2$), 5.25 (1H, d, *J* = 1.38 Hz, -C=C**H**$_2$), 5.87 (1H, brs, -C=C**H**-) ppm;

^{13}C NMR (125 MHz, $CDCl_3$): δ 12.7 (-CH-**C**H$_3$), 14.8 (-C-**C**H$_3$), 18.0 (-C-**C**H$_3$), 30.9 (-C(**C**H$_3$)$_3$), 32.5 (-**C**(CH$_3$)$_3$), 41.2 (-**C**H-CH$_3$), 64.7 (-**C**H$_2$OH), 78.8 (-**C**HOH), 112.7 (-C=**C**H$_2$), 130.9 (-**C**=CH-), 131.3 (-C=**C**H-), 134.3 (-**C**=CH-), 140.0 (-C=**C**H-), 151.4 (-**C**=CH$_2$) ppm;

IR (neat, cm^{-1}): 3354, 2958, 1713, 1651, 1644;

HRMS (EI) m/z (M^+): obsd 252.2103, calcd 252.2089 for $C_{16}H_{28}O_2$.

Syn-(5*E*,7*E*)-2-((*tert*-butyldiphenylsilyloxy)methyl)-3,5,7,9,9-pentamethyldeca-1,5,7-trien-4-ol (63)



To a solution of *syn* **62** (0.73 g, 2.89 mmol) in anhydrous DMF (9 mL) was added imidazole (0.40 g, 5.78 mmol) and tert-butyldiphenylsilyl chloride (0.85 mL, 3.18 mmol) at 0 °C under N_2. The mixture was stirred at 0 °C to room temperature for 1.5h. After completion, the mixture was poured into water and extracted with ethyl acetate (x3). The combined organic extract was washed with brine, dried ($MgSO_4$),

concentrated and purified by flash chromatography on silica gel to afford **63** as a colorless oil, 1.36 g (96%).

$\mathbf{R}_f$ 0.46 (hexane/ethyl acetate, 4:1);

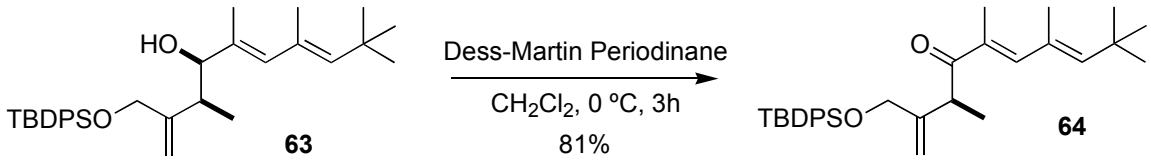
^{1}H NMR (300 MHz, $CDCl_3$): δ 1.01 (3H, d, *J* = 6.96 Hz, -CH-C**H**$_3$), 1.06 (9H, s, -C(C**H**$_3$)$_3$), 1.14 (9H, s, -C(C**H**$_3$)$_3$), 1.67 (3H, d, *J* = 1.05 Hz, -C-C**H**$_3$), 1.79 (3H, d, *J* = 1.38 Hz, -C-C**H**$_3$), 2.50 (1H, dq, *J* = 6.96, 4.5 Hz, -C**H**-CH$_3$), 3.97 (1H, d, *J* = 4.5 Hz, -C**H**-OH), 4.12 (1H, d, *J* = 13.6 Hz, -C**H**$_2$-O-), 4.19 (1H, d, *J* = 13.6 Hz, -C**H**$_2$-O-), 5.00 (1H, s, -C=C**H**$_2$), 5.26 (2H, d, J = 1.41 Hz, -C=C**H**-, -C=C**H**$_2$), 5.88 (1H, s, -C=C**H**-), 7.38-7.44 (6H, m, -Ph-**H**), 7.66-7.70 (4H, m, -Ph-**H**) ppm;

^{13}C NMR (75 MHz, $CDCl_3$): δ 13.0 (-**C**H$_3$), 14.6 (-**C**H$_3$), 18.0 (-**C**H$_3$), 19.2 (-**C**(CH$_3$)$_3$), 26.8 (-C(**C**H$_3$)$_3$), 29.6 (-**C**(CH$_3$)$_3$), 30.9 (-C(**C**H$_3$)$_3$), 40.1 (-**C**HCH$_3$), 65.9 (-**C**H$_2$OTBDPS), 77.8 (-**C**HOH), 111.2 (-C=**C**H$_2$), 127.7 (-Ph-**C**), 129.7 (-Ph-**C**), 131.0 (-C=**C**H-), 131.3 (-**C**=CH-), 133.4 (-Ph-**C**), 134.1 (-C=**C**H-), 135.5 (-Ph-**C**), 139.8 (-**C**=CH-), 150.5 (-**C**=CH$_2$) ppm;

IR (neat, cm^{-1}): 3434, 2929, 1646;

HRMS (EI) m/z [(M-C_4H_9)$^+$]: obsd 433.2535, calcd 433.2563 for $C_{28}H_{37}O_2Si$.

(5*E*,7*E*)-2-((*tert*-butyldiphenylsilyloxy)methyl)-3,5,7,9,9-pentamethyldeca-1,5,7-trien-4-one (64)



To a solution of Dess-Martin reagent (1.75 g, 4.12 mmol) in anhydrous CH_2Cl_2 (15 mL) was added dropwise of **63** (1.35 g, 2.75 mmol) prediluted in CH_2Cl_2 (5 mL) at 0 °C. The reaction mixture was stirred under nitrogen at 0 °C for 3h. After completion, the reaction mixture was diluted with ether and poured slowly into a $Na_2S_2O_3$:

$NaHCO_3$ (1:1) solution and stirred for 10 minutes and extract with ether. The combine etherate layer was washed with $NaHCO_3$, brine and dried over anhydrous $MgSO_4$. Solvent was removed in *vacuo*. The residue was purified by flash chromatography on silica gel to provide **64** as a colorless oil, 1.09 g (81%).

R_f 0.66 (hexane/ethyl acetate, 4:1);

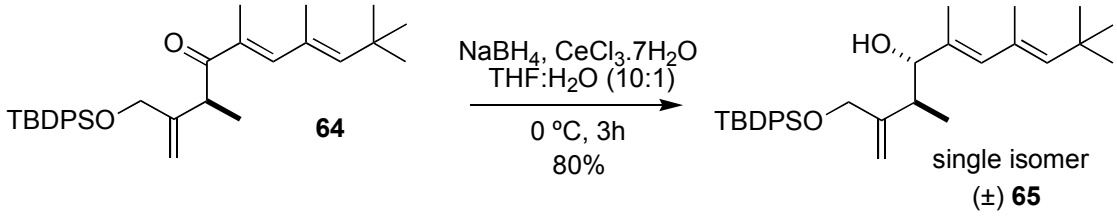
^{1}H NMR (300 MHz, $CDCl_3$): δ 1.09 (9H, s, -C(C**H**$_3$)$_3$), 1.17 (9H, s, -C(C**H**$_3$)$_3$), 1.22 (3H, d, *J* = 6.96 Hz, -CH-C**H**$_3$), 1.88 (3H, d, *J* = 1.05 Hz, -C-C**H**$_3$), 1.91 (3H, d, *J* = 1.05 Hz, -C-C**H**$_3$), 4.03 (1H, q, *J* = 6.96 Hz, -C**H**-CH$_3$), 4.16 (1H, d, *J* = 13.5 Hz, -C**H**$_2$-O-), 4.22 (1H, d, *J* = 13.5 Hz, -C**H**$_2$-O-), 4.93 (1H, brs, -C=C**H**$_2$), 5.23 (1H, d, *J* = 1.05 Hz, -C=C**H**$_2$-), 5.54 (1H, brs, -C=C**H**-), 6.99 (1H, brs, -C=C**H**-), 7.36-7.44 (6H, m, -Ph-**H**), 7.68-7.70 (4H, m, -Ph-**H**) ppm;

^{13}C NMR (75 MHz, $CDCl_3$): δ 13.4 (-**C**H$_3$), 16.9 (-**C**H$_3$), 17.4 (-**C**H$_3$), 19.2 (-**C**(CH$_3$)$_3$), 26.8 (-C(**C**H$_3$)$_3$), 30.6 (-C(**C**H$_3$)$_3$), 32.9 (-**C**(CH$_3$)$_3$), 42.4 (-**C**HCH$_3$), 65.8 (-**C**H$_2$OTBDPS), 111.1 (-C=**C**H$_2$), 127.7 (-Ph-**C** x4), 129.7 (-Ph-**C** x2), 130.9 (Ph-C*q* x2), 133.3 (-**C**=CH), 133.7 (-**C**=CH), 135.4 (-Ph-**C** x4), 144.9 (-C=**C**H-), 145.3 (-C=**C**H-), 148.4 (-**C**=CH$_2$), 203.1 (-**C**=O) ppm;

IR (neat, cm^{-1}): 2960, 1663, 1648, 1634;

HRMS (EI) m/z (M$^+$): obsd 488.3092, calcd 488.3111 for $C_{32}H_{44}O_2Si$.

***Anti*-(5*E*,7*E*)-2-((*tert*-butyldiphenylsilyloxy)methyl)-3,5,7,9,9-pentamethyldeca-1,5,7-trien-4-ol (65)**



To a solution of **64** (490 mg, 1 mmol) in THF:H_2O (10:1) (5 mL) was added $CeCl_3.7H_2O$ (130 mg, 1.5 mmol) at 0 °C. After the mixture was stirred at 0 °C for 15 minutes, $NaBH_4$ (60 mg, 1.5 mmol) was added and the reaction was stirred for 3h. After the reaction was completed (monitored by TLC), THF was removed under *vacuo*. H_2O was added and the mixture was extracted with ether. The combined etherate layer was washed with brine, dried over $MgSO_4$, concentrated and purified through flash chromatography on silica gel to afford **65** as a colorless oil, 396 mg (80%). (*anti:syn* > 99:1)

R_f 0.46 (hexane/ethyl acetate, 4:1);

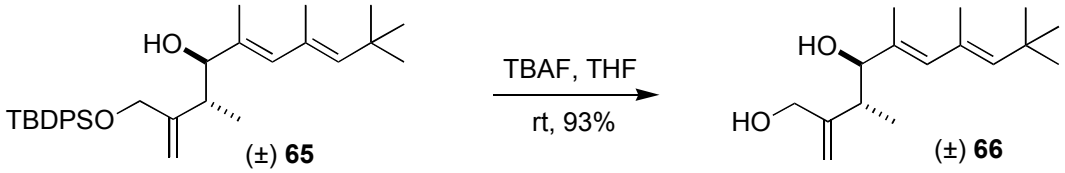
^{1}H NMR (300 MHz, $CDCl_3$): δ 0.87 (3H, d, *J* = 6.96 Hz, -CH-C**H**$_3$), 1.07 (9H, s, -C(C**H**$_3$)$_3$), 1.13 (9H, s, -C-(C**H**$_3$)$_3$), 1.71 (3H, d, *J* = 1.40 Hz, -C-C**H**$_3$), 1.79 (3H, d, *J* = 1.05 Hz, -C-C**H**$_3$), 2.39 (1H, dq, *J* = 9.40, 6.96 Hz, -C**H**-CH$_3$), 3.80 (1H, dd, *J* = 9.40, 2.45 Hz, -C**H**-OH), 4.14 (2H, s, -C**H**$_2$-O-), 5.09 (1H, s, -C=C**H**$_2$), 5.30 (1H, d, *J* = 1.40 Hz, -C=C**H**$_2$-), 5.32 (1H, d, *J* = 1.40 Hz, -C=C**H**-), 5.80 (1H, s, -C=C**H**-), 7.36-7.44 (6H, m, -Ph-**H**), 7.69-7.72 (4H, m, -Ph-**H**) ppm;

^{13}C NMR (75 MHz, $CDCl_3$): δ 11.9 (-**C**H$_3$), 17.5 (-**C**H$_3$), 17.9 (-**C**H$_3$), 19.1 (-**C**(CH$_3$)$_3$), 26.8 (-C(**C**H$_3$)$_3$), 29.6 (-**C**(CH$_3$)$_3$), 30.9 (-C(**C**H$_3$)$_3$), 41.8 (-**C**HCH$_3$), 66.0 (-**C**H$_2$OTBDPS), 82.0 (-**C**HOH), 111.2 (-C=**C**H$_2$), 127.7 (-Ph-**C** x4), 129.8 (-Ph-**C** x2), 130.6 (-C=**C**H-), 133.1 (Ph-C*q* x2), 134.1 (-**C**=CH), 134.3 (-C=**C**H-), 135.6 (-Ph-**C** x4), 140.2 (-**C**=CH), 150.3 (-**C**=CH$_2$) ppm;

IR (neat, cm^{-1}): 3428, 2957, 2930, 1649, 1558;

HRMS (EI) m/z [(M-C_4H_9)$^+$]: obsd 433.2535, calcd 433.2563 for $C_{28}H_{37}O_2Si$.

***Anti*-(5*E*,7*E*)-3,5,7,9,9-pentamethyl-2-methylenedeca-5,7-diene-1,4-diol (66)**



To a solution of **65** (0.5 g, 1.02 mmol) in THF (2 mL) was added TBAF (1.5 mL, 1.0 M in THF, 1.5 mmol). The mixture was stirred for 30 minutes at room temperature. After the reaction was completed (monitored by TLC), the mixture was concentrated in *vacuo* to remove the THF. The residue was purified by flash chromatography on silica gel to afford **66** as a colorless oil, 0.24 g (93%).

$\mathbf{R}_f$ 0.40 (hexane/ethyl acetate, 2:1);

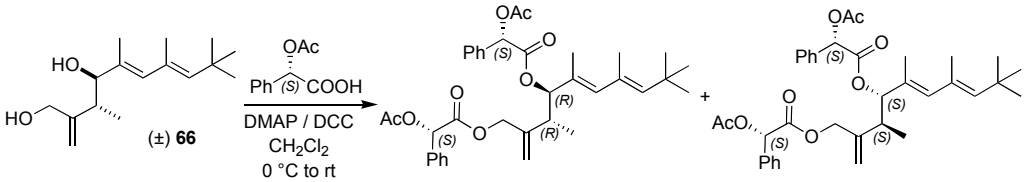
^{1}H NMR (500 MHz, $CDCl_3$): δ 0.94 (3H, d, *J* = 6.95 Hz, -CH-C**H**$_3$), 1.13 (9H, s, -C(C**H**$_3$)$_3$), 1.73 (3H, d, *J* = 1.4 Hz, -C-C**H**$_3$), 1.81 (3H, d, *J* = 0.95 Hz, -C-C**H**$_3$), 2.27 (2H, brs, -CH$_2$O**H**, -CHO**H**), 2.48 (1H, dq, *J* = 9.25, 6.95 Hz, -C**H**-CH$_3$), 3.82 (1H, d, *J* = 9.25 Hz, -C**H**-OH), 4.10 (1H, dd, *J* = 12.47, 0.95 Hz, -C**H**$_2$-OH), 4.15 (1H, dd, *J* = 12.47, 0.95 Hz, -C**H**$_2$-OH), 5.05 (1H, s, -C=C**H**-), 5.19 (1H, d, *J* = 0.95 Hz, -C=C**H**$_2$), 5.31 (1H, d, *J* = 0.95 Hz, -C=C**H**$_2$), 5.83 (1H, s, -C=C**H**-) ppm;

^{13}C NMR (125 MHz, $CDCl_3$): δ 12.1 (-CH-**C**H$_3$), 17.6 (-C-**C**H$_3$), 17.9 (-C-**C**H$_3$), 30.9 (-C(**C**H$_3$)$_3$), 32.6 (-**C**(CH$_3$)$_3$), 41.2 (-**C**H-CH$_3$), 65.6 (-**C**H$_2$OH), 83.1 (-**C**HOH), 112.8 (-C=**C**H$_2$), 130.7 (-**C**=CH-), 134.3 (-**C**=CH-), 134.5 (-C=**C**H-), 140.6 (-C=**C**H-), 151.5 (-**C**=CH$_2$) ppm;

IR (neat, cm^{-1}): 3353, 2958, 1743, 1643;

HRMS (ESI) m/z (M^+-1): obsd 251.2011, calcd 252.2011 for $C_{16}H_{27}O_2$.

(1*S*,1'*S*)-2,2'-((3*R*,4*R*,5*E*,7*E*)-3,5,7,9,9-pentamethyl-2-methylenedeca-5,7-diene-1,4-diyl)bis(oxy)bis(2-oxo-1-phenylethane-2,1-diyl) diacetate (*R,R*)-B and (1*S*,1'*S*)-2,2'-((3*S*,4*S*,5*E*,7*E*)-3,5,7,9,9-pentamethyl-2-methylenedeca-5,7-diene-1,4-diyl)bis(oxy)bis(2-oxo-1-phenylethane-2,1-diyl) diacetate (*S,S*)-C



(*R,R*)-B $[\alpha]^{25}_{D}$ = +55° (c = 4.0, $CHCl_3$) **(*S,S*)-C** $[\alpha]^{26}_{D}$ = +62° (c = 3.2, $CHCl_3$)

To a mixture of *anti* (±)-66 (0.24 g, 0.95 mmol), *S*-(+)-α-acetoxyphenylacetic acid (0.56 g, 2.85 mmol) and DMAP (12 mg, 0.095 mmol) in dried CH_2Cl_2 (4 mL) was added DCC (0.39 g, 1.9 mmol) prediluted in 1 mL CH_2Cl_2 dropwise at 0 °C. The reaction mixture was stirred at room temperature for 12h. After completion, CH_2Cl_2 was removed *via* rotary evaporator and the crude product was directly subjected to column chromatography. Purification by flash chromatography on silica gel (Hex:CH_2Cl_2:EA (3:3:0.2) afforded two pure enantiomers as colorless oil with 96% overall yield.

(*R,R*)-B

R_f 0.36 (hexane/CH_2Cl_2/ethyl acetate, 3:3:0.25);

$[\alpha]^{25}_{D}$ = +55.4° (*c* = 4.0 , $CHCl_3$);

^{1}H NMR (500 MHz, $CDCl_3$): δ 0.72 (3H, d, *J* = 7.4 Hz, -CH-C**H**$_3$), 1.12 (9H, s, -C(C**H**$_3$)$_3$), 1.64 (3H, d, *J* = 1.4 Hz, -C-C**H**$_3$), 1.76 (3H, d, *J* = 1.35 Hz, -C-C**H**$_3$), 2.14 (3H, s, -O**Ac**), 2.19 (3H, s, -O**Ac**), 2.33 (1H, dq, *J* = 9.7, 7.4 Hz, -C**H**-CH$_3$), 4.11 (1H, d, *J* = 12.95 Hz, -C**H**$_2$-O-), 4.19 (1H, d, *J* = 12.95 Hz, -C**H**$_2$-O-), 4.62 (1H, s, -C=C**H**$_2$-), 4.68 (1H, s, -C=C**H**$_2$), 4.99 (1H, d, *J* = 9.7 Hz, -C**H**-O-), 5.24 (1H, t, *J* = 1.35 Hz, -C=C**H**-), 5.85 (1H, s, -C=C**H**-), 5.87 (1H, s, -C**H**-OAc), 5.92 (1H, s, -C**H**-OAc), 7.26-7.27 (3H, m, -Ph-**H**), 7.33-7.35 (2H, m, -Ph-**H**), 7.38-7.39 (3H, m, -Ph-**H**), 7.45-7.47 (2H, m, -Ph-**H**) ppm;

^{13}C NMR (125 MHz, $CDCl_3$): δ 12.7 (-C-**C**H_3), 16.9 (O**Ac**), 17.7 (OAc), 20.6 (-C-**C**H_3), 30.8 (-C(**C**$H_3)_3$), 32.5 (-**C**$(CH_3)_3$), 38.9 (-**C**H-CH_3), 67.3 (-**C**H_2O-), 74.3 (-**C**H-OAc), 74.4 (-**C**H-OAc), 84.2 (-**C**H-O-), 114.5 (-C=**C**H_2), 127.6 (-Ph-C*m*), 127.7 (-Ph-C*m*), 128.5 (-Ph-C*o*), 128.7 (-Ph-C*o*), 129.0 (-Ph-C*p*), 129.2 (-Ph-C*p*), 129.4 (-HC=**C**-CH_3), 130.3 (-HC=**C**-CH_3), 133.7 (-Ph-C*q*), 134.0 (-Ph-C*q*), 136.3 (-**C**H=C-CH_3), 140.8 (-**C**H=C-CH_3), 143.9 (-**C**=CH_2), 167.6 (**C**=O), 168.3 (**C**=O), 169.9 (**C**=O), 170.1 (**C**=O) ppm;

HRMS (ESI) m/z $(M+Na)^+$: obsd. 627.2928, calcd 627.2934 for $C_{36}H_{44}NaO_8$;

(*S*,*S*)-C

R_f 0.27 (hexane/CH_2Cl_2/ethyl acetate, 3:3:0.25);

$[\alpha]^{26}_D$ = +62.2° (*c* = 3.2, $CHCl_3$);

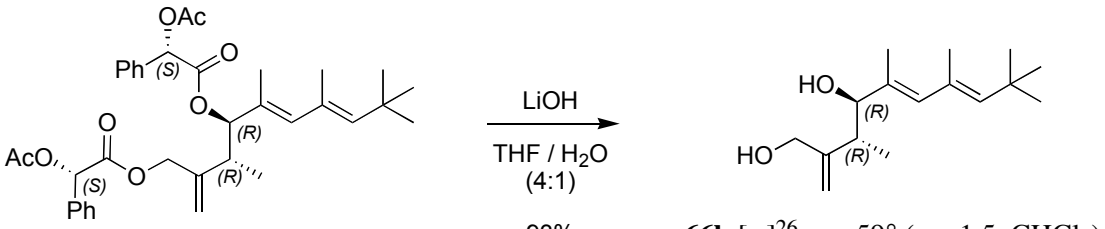
^{1}H NMR (500 MHz, $CDCl_3$): δ 0.82 (3H, d, *J* = 6.95 Hz, -CH-C**H**$_3$), 1.09 (9H, s, -C(C**H**$_3)_3$), 1.28 (3H, d, *J* = 1.4 Hz, -C-C**H**$_3$), 1.64 (3H, d, *J* = 0.95 Hz, -C-C**H**$_3$), 2.15 (3H, s, -O**Ac**), 2.20 (3H, s, -O**Ac**), 2.35 (1H, dq, *J* = 9.75, 6.95 Hz, -C**H**-CH_3), 4.57 (1H, d, *J* = 12.95 Hz, -C**H**$_2$-O-), 4.66 (1H, d, *J* = 12.95 Hz, -C**H**$_2$-O-), 4.95 (1H, d, *J* = 9.75 Hz, -C**H**-O-), 4.98 (1H, s, -C=C**H**$_2$-), 5.01 (1H, s, -C=C**H**$_2$), 5.06 (1H, t, *J* = 1.4 Hz, -C=C**H**-), 5.62 (1H, s, -C=C**H**-), 5.88 (1H, s, -C**H**-OAc), 5.98 (1H, s, -C**H**-OAc), 7.32-7.34 (3H, m, -Ph-**H**), 7.36-7.39 (5H, m, -Ph-**H**), 7.48-7.50 (2H, m, -Ph-**H**) ppm;

^{13}C NMR (125 MHz, $CDCl_3$): δ 12.4 (-C-**C**H_3), 16.7 (O**Ac**), 17.5 (OAc), 20.6 (-C-**C**H_3), 30.8 (-C(**C**$H_3)_3$), 32.5 (-**C**$(CH_3)_3$), 38.4 (-**C**H-CH_3), 67.9 (-**C**H_2O-), 74.3 (-**C**H-OAc), 74.5 (-**C**H-OAc), 84.5 (-**C**H-O-), 114.5 (-C=**C**H_2), 127.6 (-Ph-C*m*), 127.7 (-Ph-C*m*), 128.5 (-Ph-C*o*), 128.7 (-Ph-C*o*), 129.0 (-Ph-C*p*), 129.2 (-Ph-C*p*), 129.4, (-HC=**C**-CH_3), 130.3 (-HC=**C**-CH_3), 133.7 (-Ph-C*q*), 134.0 (-Ph-C*q*), 136.3 (-**C**H=C-

CH_3), 140.8 (-**C**H=C-CH_3), 143.9 (-**C**=CH_2), 167.6 (**C**=O), 168.2 (**C**=O), 169.9 (**C**=O), 170.1 (**C**=O) ppm;

HRMS (ESI) m/z $(M+Na)^+$: obsd 627.2928, calcd 627.2934 for $C_{36}H_{44}NaO_8$.

***Anti*-(3*R*,4*R*,5*E*,7*E*)-3,5,7,9,9-pentamethyl-2-methylenedeca-5,7-diene-1,4-diol (66b)**



(***R*,*R***)-**B** **66b** $[\alpha]^{26}_D$ = -59° (*c* = 1.5, $CHCl_3$)

To a solution of (*R,R*)-**B** (40 mg, 0.066 mmol) in THF (1 mL) at 0 °C was added a solution of LiOH (6 mg, 0.14 mmol) in water (1 mL). The resulting mixture was stirred at room temperature for 12h prior to workup. The mixture was extracted with ethyl acetate (x5). The combined organic extract was dried over anhydrous Na_2SO_4, filtered and concentrated to afford the desired product **66b** as a white amorphous solid, 15.6 mg (93%).

$\mathbf{R}_f$ 0.40 (hexane/ethyl acetate, 2:1);

$[\alpha]^{26}_D$ = -59° (*c* = 1.5, $CHCl_3$);

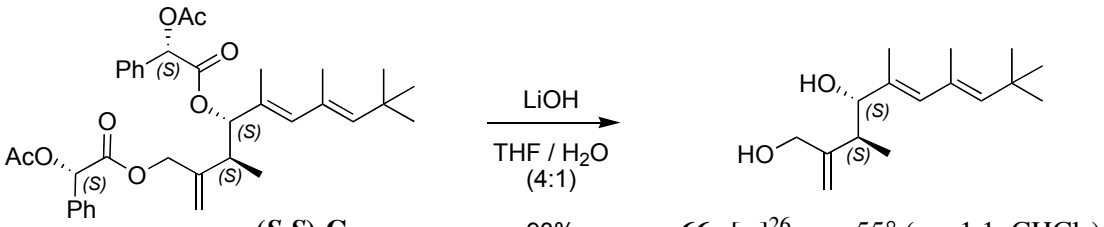
^{1}H NMR (500 MHz, $CDCl_3$): δ 0.94 (3H, d, *J* = 6.95 Hz, -CH-C**H**$_3$), 1.13 (9H, s, -C(C**H**$_3$)$_3$), 1.73 (3H, d, *J* = 1.4 Hz, -C-C**H**$_3$), 1.81 (3H, d, *J* = 0.95 Hz, -C-C**H**$_3$), 2.27 (2H, brs, -CH_2O**H**, -CHO**H**), 2.48 (1H, dq, *J* = 9.25, 6.95 Hz, -C**H**-CH_3), 3.82 (1H, d, *J* = 9.25 Hz, -C**H**-OH), 4.10 (1H, dd, *J* = 12.47, 0.95 Hz, -C**H**$_2$-OH), 4.15 (1H, dd, *J* = 12.47, 0.95 Hz, -C**H**$_2$-OH), 5.05 (1H, s, -C=C**H**-), 5.19 (1H, d, *J* = 0.95 Hz, -C=C**H**$_2$), 5.31 (1H, d, *J* = 0.95 Hz, -C=C**H**$_2$), 5.83 (1H, s, -C=C**H**-) ppm;

^{13}C NMR (125 MHz, $CDCl_3$): δ 12.1 (-CH-**C**H_3), 17.6 (-C-**C**H_3), 17.9 (-C-**C**H_3), 30.9 (-C(**C**$H_3)_3$), 32.6 (-**C**$(CH_3)_3$), 41.2 (-**C**H-CH_3), 65.6 (-**C**H_2OH), 83.1 (-**C**HOH), 112.8 (-C=**C**H_2), 130.7 (-**C**=CH-), 134.3 (-**C**=CH-), 134.5 (-C=**C**H-), 140.6 (-C=**C**H-), 151.5 (-**C**=CH_2) ppm;

IR (neat, cm^{-1}): 3353, 2958, 1743, 1643;

HRMS (ESI) m/z (M^+-1): obsd 251.2011, calcd 251.2011 for $C_{16}H_{27}O_2$.

***Anti*-(3*S*,4*S*,5*E*,7*E*)-3,5,7,9,9-pentamethyl-2-methylenedeca-5,7-diene-1,4-diol (66c)**



(*S*,*S*)-C 93% **66c** $[\alpha]^{26}_D$ = +55° (*c* = 1.1, $CHCl_3$)

Follow the same hydrolysis procedure for **66b**, **66c** was obtained as a white amorphous solid in 93% yield.

R_f 0.40 (hexane/ethyl acetate, 2:1);

$[\alpha]^{26}_D$ = +55° (*c* = 1.1, $CHCl_3$);

^{1}H NMR (500 MHz, $CDCl_3$): δ 0.94 (3H, d, *J* = 6.95 Hz, -CH-C**H**$_3$), 1.13 (9H, s, -C(C**H**$_3)_3$), 1.73 (3H, d, *J* = 1.4 Hz, -C-C**H**$_3$), 1.81 (3H, d, *J* = 0.95 Hz, -C-C**H**$_3$), 2.27 (2H, brs, -CH_2O**H**, -CHO**H**), 2.48 (1H, dq, *J* = 9.25, 6.95 Hz, -C**H**-CH_3), 3.82 (1H, d, *J* = 9.25 Hz, -C**H**-OH), 4.10 (1H, dd, *J* = 12.47, 0.95 Hz, -C**H**$_2$-OH), 4.15 (1H, dd, *J* = 12.47, 0.95 Hz, -C**H**$_2$-OH), 5.05 (1H, s, -C=C**H**-), 5.19 (1H, d, *J* = 0.95 Hz, -C=C**H**$_2$), 5.31 (1H, d, *J* = 0.95 Hz, -C=C**H**$_2$), 5.83 (1H, s, -C=C**H**-) ppm;

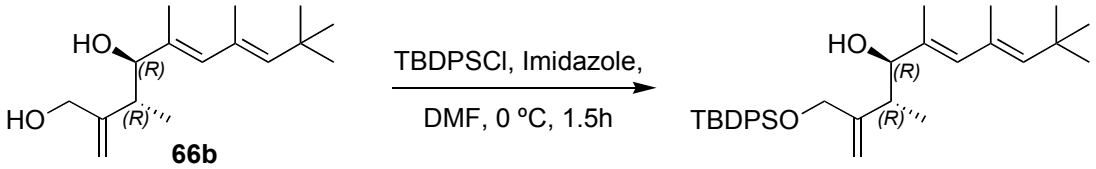
^{13}C NMR (125 MHz, $CDCl_3$): δ 12.1 (-CH-**C**H_3), 17.6 (-C-**C**H_3), 17.9 (-C-**C**H_3), 30.9 (-C(**C**$H_3)_3$), 32.6 (-**C**$(CH_3)_3$), 41.2 (-**C**H-CH_3), 65.6 (-**C**H_2OH), 83.1 (-**C**HOH), 112.8

(-C=**C**H_2), 130.7 (-**C**=CH-), 134.3 (-**C**=CH-), 134.5 (-C=**C**H-), 140.6 (-C=**C**H-), 151.5 (-**C**=CH_2) ppm;

IR (neat, cm^{-1}): 3353, 2958, 1743, 1643;

HRMS (ESI) m/z (M^+-1): obsd 251.2011, calcd 251.2011 for $C_{16}H_{27}O_2$.

(3*R*,4*R*,5*E*,7*E*)-2-((*tert*-butyldiphenylsilyloxy)methyl)-3,5,7,9,9-pentamethyldeca-1,5,7-trien-4-ol (65b)



65b $[\alpha]^{26}_D$ = -19° (*c* = 0.7, $CHCl_3$)

Follow the same protecting procedure for **63**, **65b** was obtained as colorless oil.

R_f 0.46 (hexane/ethyl acetate, 4:1);

$[\alpha]^{26}_D$ = -19° (*c* = 0.7 , $CHCl_3$);

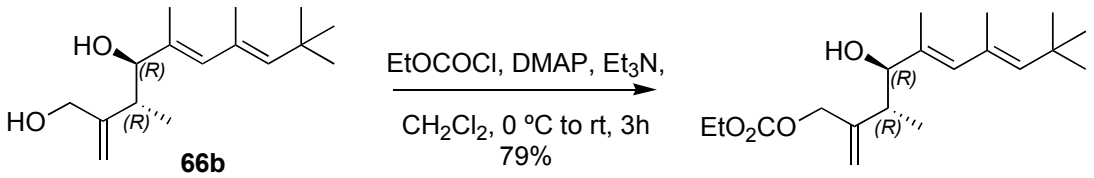
^{1}H NMR (300 MHz, $CDCl_3$): δ 0.87 (3H, d, *J* = 6.96 Hz, -CH-C**H**$_3$), 1.07 (9H, s, -C(C**H**$_3$)$_3$), 1.13 (9H, s, -C-(C**H**$_3$)$_3$), 1.71 (3H, d, *J* = 1.40 Hz, -C-C**H**$_3$), 1.79 (3H, d, *J* = 1.05 Hz, -C-C**H**$_3$), 2.39 (1H, dq, *J* = 9.40, 6.96 Hz, -C**H**-CH_3), 3.80 (1H, dd, *J* = 9.40, 2.45 Hz, -C**H**-OH), 4.14 (2H, s, -C**H**$_2$-O-), 5.09 (1H, s, -C=C**H**$_2$), 5.30 (1H, d, *J* = 1.40 Hz, -C=C**H**$_2$-), 5.32 (1H, d, *J* = 1.40 Hz, -C=C**H**-), 5.80 (1H, s, -C=C**H**-), 7.36-7.44 (6H, m, -Ph-**H**), 7.69-7.72 (4H, m, -Ph-**H**) ppm;

^{13}C NMR (75 MHz, $CDCl_3$): δ 11.9 (-**C**H_3), 17.5 (-**C**H_3), 17.9 (-**C**H_3), 19.1 (-**C**$(CH_3)_3$), 26.8 (-C(**C**$H_3)_3$), 29.6 (-**C**$(CH_3)_3$), 30.9 (-C(**C**$H_3)_3$), 41.8 (-**C**HCH_3), 66.0 (-**C**H_2OTBDPS), 82.0 (-**C**HOH), 111.2 (-C=**C**H_2), 127.7 (-Ph-**C** x4), 129.8 (-Ph-**C** x2), 130.6 (-C=**C**H-), 133.1 (Ph-C*q* x2), 134.1 (-**C**=CH), 134.3 (-C=**C**H-), 135.6 (-Ph-**C** x4), 140.2 (-**C**=CH), 150.3 (-**C**=CH_2) ppm;

IR (neat, cm^{-1}): 3428, 2957, 2930, 1649, 1558;

HRMS (EI) m/z [(M-C_4H_9)$^+$]: obsd 433.2535, calcd 433.2563 for $C_{28}H_{37}O_2Si$.

***Anti*-ethyl (3*R*,4*R*,5*E*,7*E*)-4-hydroxy-3,5,7,9,9-pentamethyl-2-methylenedeca-5,7-dienyl carbonate (67b)**



67b $[\alpha]^{27}_{D}$ = -14° (c = 4.2, $CHCl_3$)

To a solution of *anti* **66b** (0.31 g, 1.23 mmol), anhydrous triethyl amine (0.51 mL, 3.69 mmol) and DMAP (0.15 g, 1.23 mmol) in CH_2Cl_2 (12 ml) at 0 °C was added ethyl chloroformate (0.117 ml, 1.23 mmol) dropwise. The reaction progress was monitored by TLC. After completion, the reaction mixture was poured into ice water and extracted with ethyl acetate (x3). The combined organic extracts were washed with $NaHCO_3$, brine, dried ($MgSO_4$) and concentrated in *vacuo*. Purification by flash chromatography on silica gel afforded **67b** as colorless oil, 0.31 g (79%).

$\mathbf{R}_f$ 0.42 (hexane/ethyl acetate, 4:1);

$[\alpha]^{27}_{D}$ = -14° (*c* = 4.2, $CHCl_3$);

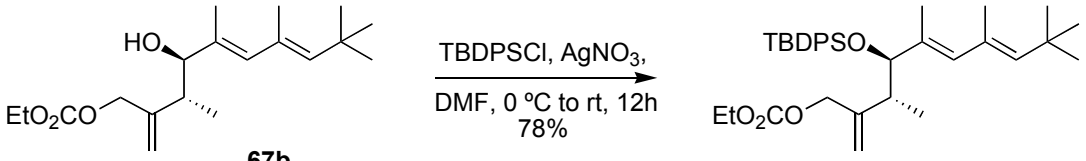
^{1}H NMR (500 MHz, $CDCl_3$): δ 0.95 (3H, d, *J* = 7.40 Hz, -CH-C**H**$_3$), 1.14 (9H, s, -C(C**H**$_3$)$_3$), 1.31 (3H, t, *J* = 6.95 Hz, -OCH$_2$-C**H**$_3$), 1.73 (3H, d, *J* = 1.40 Hz, -C-C**H**$_3$), 1.81 (3H, d, *J* = 1.40 Hz, -C-C**H**$_3$), 2.45 (1H, dq, *J* = 9.25, 7.4 Hz, -C**H**-CH$_3$), 3.85 (1H, d, *J* = 9.25, 1.85 Hz, -C**H**OH), 4.21 (2H, q, *J* = 6.95 Hz, -C**H**$_2$-CH$_3$-), 4.66 (2H, s, -C**H**$_2$-O-), 5.15 (1H, s, -C=C**H**$_2$), 5.25 (1H, d, *J* = 0.95 Hz, -C=C**H**$_2$), 5.31 (1H, d, *J* = 0.95 Hz, -C=C**H**-), 5.83 (1H, s, -C=C**H**-) ppm;

^{13}C NMR (75 MHz, $CDCl_3$): δ 11.9 (-**C**H$_3$), 14.2 (-**C**H$_3$), 16.9 (-**C**H$_3$), 17.8 (-**C**H$_3$), 30.9 (-C(**C**H$_3$)$_3$), 32.5 (-**C**(CH$_3$)$_3$), 41.8 (-**C**HCH$_3$), 64.1 (-O**C**H$_2$CH$_3$), 68.7 (-**C**H$_2$OCO$_2$Et), 81.8 (-**C**HOH), 113.9 (-C=**C**H$_2$), 130.6 (-HC=**C**-), 133.9 (-HC=**C**-), 134.4 (-C=**C**H-), 140.4 (-C=**C**H-), 145.9 (-**C**=CH$_2$), 155.0 (**C**=O) ppm;

IR (neat, cm^{-1}): 3500, 2959, 1747, 1732, 1651;

HRMS (EI) m/z (M^+): obsd 324.2295, calcd 324.2310 for $C_{19}H_{32}O_4$.

***Anti*-(3*R*,4*R*,5*E*,7*E*)-4-(*tert*-butyldiphenylsilyloxy)-3,5,7,9,9-pentamethyl-2-methylenedeca-5,7-dienyl ethyl carbonate (68b)**



67b **68b** $[\alpha]^{27}_D = +7°$ (c = 5.4, $CHCl_3$)

To a solution of **67b** (0.2 g, 0.6 mmol) in 1 mL DMF was added $AgNO_3$ (0.2 g, 1.2 mmol) followed by TBDPSCl (0.18 mL, 0.66 mmol). After the reaction was completed (monitored by TLC), the reaction mixture was poured into ice water and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous $MgSO_4$, concentrated in *vacuo* and purified by flash chromatography to afford **68b** as a colorless oil, 0.263 g (78%).

R_f 0.55 (hexane/ethyl acetate, 4:1);

$[\alpha]^{27}_D = +7°$ (c = 5.4, $CHCl_3$);

^{1}H NMR (500 MHz, $CDCl_3$): δ 0.84 (3H, d, J = 7.35 Hz, -CH-C**H**$_3$), 1.02 (9H, s, -C(C**H**$_3$)$_3$), 1.08 (9H, s, -C(C**H**$_3$)$_3$), 1.31 (3H, t, J = 6.95 Hz, -OCH$_2$C**H**$_3$), 1.55 (3H, s, -C-C**H**$_3$), 1.57 (3H, dd, J = 4.15, 1.4 Hz, -C-C**H**$_3$), 2.42 (1H, dq, J = 8.30, 7.35 Hz, -C**H**-CH$_3$), 3.94 (1H, d, J = 8.30 Hz, -C**H**-O-), 4.19 (2H, q, J = 6.95 Hz, -OC**H**$_2$CH$_3$), 4.43 (1H, d, J = 13.45 Hz, -C**H**$_2$OCO$_2$Et), 4.52 (1H, d, J = 13.45 Hz, -C**H**$_2$OCO$_2$Et), 4.91 (1H, s, -C=C**H**$_2$-), 4.98 (1H, t, J = 1.40 Hz, -C=C**H**-), 5.08 (1H, d, J = 0.95 Hz, -C=C**H**$_2$-), 5.39 (1H, s, -C=C**H**-), 7.28-7.41 (6H, m, -Ph-**H**), 7.58-7.64 (4H, m, -Ph-**H**) ppm;

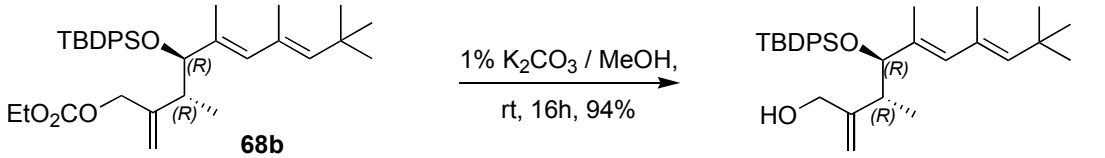
^{13}C NMR (75 MHz, $CDCl_3$): δ 13.0 (-**C**H$_3$), 14.2 (-**C**H$_3$), 16.9 (-**C**H$_3$), 17.6 (-**C**H$_3$), 19.4 (-**C**(CH$_3$)$_3$), 27.1 (-C(**C**H$_3$)$_3$), 30.9 (-**C**(CH$_3$)$_3$), 32.4 (-C(**C**H$_3$)$_3$), 42.1 (-**C**HCH$_3$),

63.7 (-O**C**H_2-), 69.9 (-**C**H_2O-), 83.7 (-**C**HOTBDPS), 113.0 (-C=**C**H_2), 127.0 (Ph-**C** x4), 129.3 (Ph-**C** x2), 130.5 (-CH=**C**-),133.7 (Ph-**C***q* x2), 133.9 (-**C**=CH-), 134.2 (-C=**C**H-), 136.2 (Ph-**C** x4), 139.7 (-**C**H=C-), 145.8 (-**C**=CH_2), 154.9 (**C**=O) ppm;

IR (neat cm^{-1}): 2929, 2859, 1756, 1663;

HRMS (EI) m/z (M^+): obsd 562.3489, calcd 562.3478 for $C_{35}H_{50}O_4Si$.

***Anti*-(3*R*,4*R*,5*E*,7*E*)-4-(*tert*-butyldiphenylsilyloxy)-3,5,7,9,9-pentamethyl-2-methylenedeca-5,7-dien-1-ol (69b)**



69b $[\alpha]^{26}_D$ = +19° (*c* = 0.7, $CHCl_3$)

68b (0.25 g, 0.44 mmol) was dissolved in 1% K_2CO_3 in MeOH solution at room temperature. The solution was stirred at room temperature for 16h. After the reaction was completed (monitored by TLC), the solution was neutralized to pH=7 using 1M HCl. The mixture was extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$ and concentrated in *vacuo*. The residue was purified by flash chromatography on silica gel to afford **69b** as colorless oil, 0.20 g (94%).

R_f 0.22 (hexane/ethyl acetate, 4:1);

$[\alpha]^{26}_D$ = +19° (*c* = 0.7, $CHCl_3$);

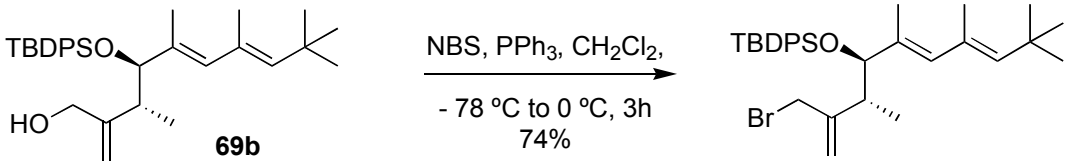
^{1}H NMR (300 MHz, $CDCl_3$): δ 0.83 (3H, d, *J* = 6.96 Hz, -CH-C**H**$_3$), 1.04 (9H, s, -C(C**H**$_3$)$_3$), 1.10 (9H, s, -C-(C**H**$_3$)$_3$), 1.59 (3H, s, -C-C**H**$_3$), 1.62 (3H, s, -C-C**H**$_3$), 2.46 (1H, dq, *J* = 8.7, 6.96 Hz, -C**H**-CH_3), 3.90 (1H, d, *J* = 14.28 Hz, -C**H**$_2$OH), 3.93 (1H, d, *J* = 8.7 Hz, -C**H**-O-), 4.03 (1H, d, *J* = 14.28 Hz, -C**H**$_2$OH), 4.84 (1H, s, -C=C**H**$_2$), 5.01 (2H, d, *J* = 1.38 Hz, -C=C**H**-,-C=C**H**$_2$), 5.38 (1H, s, -C=C**H**-), 7.29-7.43 (6H, m, -Ph-**H**), 7.60-7.68 (4H, m, -Ph-**H**) ppm;

^{13}C NMR (75 MHz, $CDCl_3$): δ 12.3 (-**C**H_3), 17.2 (-**C**H_3), 17.6 (-**C**H_3), 19.4 (-**C**$(CH_3)_3$), 27.1 (-C(**C**$H_3)_3$), 30.9 (-C(**C**$H_3)_3$), 32.4 (-**C**$(CH_3)_3$), 41.5 (-**C**HCH_3), 65.7 (-**C**H_2OTBDPS), 84.4 (-**C**HOH), 110.0 (-C=**C**H_2), 127.1 (Ph-**C** x2), 127.2 (Ph-**C** x2), 129.4 (Ph-**C** x1), 129.5 (Ph-**C** x1), 130.6 (-**C**=C-), 133.8 (-**C**=C-), 133.9 (-**C**=C-), 134.0 (-**C**=C-), 134.3 (-C=**C**H-), 136.3 (Ph-**C** x2), 136.3 (Ph-**C** x2), 139.8 (-C=**C**H-), 151.4 (-**C**=CH_2) ppm;

IR (neat cm^{-1}): 3354, 2958, 2874, 1654;

HRMS (EI) m/z (M^+): obsd 490.3288, calcd 490.3267 for $C_{32}H_{46}O_2Si$.

***Anti*-((3*R*,4*R*,5*E*,7*E*)-2-(bromomethyl)-3,5,7,9,9-pentamethyldeca-1,5,7-trien-4-yloxy)(*tert*-butyl)diphenylsilane (70b)**



70b $[\alpha]^{26}_D$ = +25° (*c* = 2.5, $CHCl_3$)

To a solution of **69b** (97.6 mg, 0.21 mmol) in anhydrous CH_2Cl_2 (3 mL) at -78 °C was added triphenyphosphine (81 mg, 0.31 mmol) in one portion. The mixture was stirred at -78 °C for 10 minutes until all the triphenylphospine dissolved and NBS (47 mg, 0.264 mmol) was added in one portion. The resulting solution was stirred at -78 °C for 30 minutes and 0 °C for 15 minutes. After all the starting material had been consumed (monitored by TLC), ether and H_2O was added in. The mixture was partitioned. The organic layer was washed with brine, dried over anhydrous $MgSO_4$ and concentrated in *vacuo*. Purification through flash chromatography on silica gel afforded **70b** as a colorless oil, 88.6 mg (74%).

R_f 0.79 (hexane/ethyl acetate; 4:1);

$[\alpha]^{26}_D$ = +25° (*c* = 2.5, $CHCl_3$);

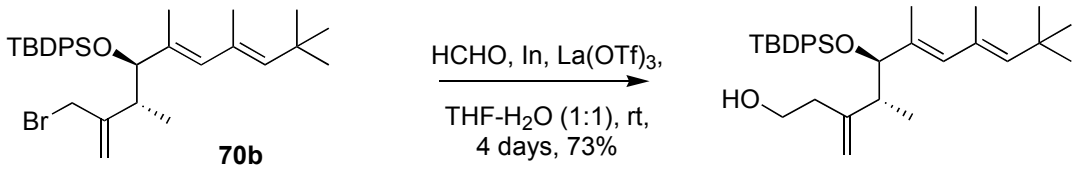
^{1}H NMR (500 MHz, $CDCl_3$): δ 0.93 (3H, d, *J* = 6.95 Hz, -CH-C**H**$_3$), 1.06 (9H, s, -C(C**H**$_3$)$_3$), 1.12 (9H, s, -C-(C**H**$_3$)$_3$), 1.60 (3H, s, -C-C**H**$_3$), 1.63 (3H, s, -C-C**H**$_3$), 2.62 (1H, dq, *J* = 8.3, 6.95 Hz, -C**H**-CH$_3$), 3.92 (1H, d, *J* = 9.75 Hz, -C**H**$_2$-Br), 3.98 (1H, d, *J* = 8.3 Hz, -C**H**-O-), 4.02 (1H, *J* = 9.75 Hz, -C**H**$_2$-Br), 4.94 (1H, s, -C=C**H**$_2$-), 5.02 (1H, s, -C=C**H**-), 5.19 (1H, s, -C=C**H**$_2$), 5.43 (1H, s, -C=C**H**-), 7.33-7.43 (6H, m, Ph-**H**), 7.62-7.67 (4H, m, Ph-**H**) ppm;

^{13}C NMR (125 MHz, $CDCl_3$): δ 13.1 (-**C**H$_3$), 17.6 (-**C**H$_3$), 17.9 (-**C**H$_3$), 27.2 (-C(**C**H$_3$)$_3$), 30.9 (-C(**C**H$_3$)$_3$), 31.9 (-**C**(CH$_3$)$_3$), 32.5 (-**C**(CH$_3$)$_3$), 38.8 (-**C**H$_2$Br), 41.9 (-**C**HCH$_3$), 84.9 (-**C**HOTBDPS), 115.6 (-C=**C**H$_2$), 127.1 (Ph-**C** x2), 127.2 (Ph-**C** x2), 129.4 (Ph-**C**), 129.5 (Ph-**C**), 130.5 (-**C**=C-), 133.8 (-**C**=C-), 133.9 (-**C**=C-), 134.1 (-**C**=C-), 134.4 (-C=**C**H-), 136.2 (Ph-**C** x2), 136.2 (Ph-**C** x2), 139.9 (-C=**C**H-), 148.7 (-**C**=CH$_2$) ppm;

IR (neat cm^{-1}): 2957, 2859, 1636, 1479;

HRMS (EI) m/z [M-(C_4H_9)$^+$]: obsd 497.1723, calcd 497.1750 for $C_{28}H_{36}OSi^{81}Br$.

***Anti*-(4*R*,5*R*,6*E*,8*E*)-5-(*tert*-butyldiphenylsilyloxy)-4,6,8,10,10-pentamethyl-3-methyleneundeca-6,8-dien-1-ol (71b)**



71b $[\alpha]^{26}_D$ = +18° (*c* = 4.1, $CHCl_3$)

To a mixture of **70b** (0.4 g, 0.72 mmol) and formaldehyde solution (35-40% in water) (1 ml) in THF (1 mL) were added indium (88 mg, 0.72 mmol) and La(OTf)$_3$ (0.42 g, 0.72 mmol). The mixture was stirred vigorously at room temperature for 4 days. After the reaction was completed (monitored by TLC), the reaction mixture was extracted with ethyl acetate. The organic extracts were combined and washed with $NaHCO_3$

solution, brine and dried over anhydrous $MgSO_4$ and concentrated in *vacuo*. The crude product was purified by flash chromatography on silica gel. Elution with 5% ethyl acetate in hexane resulted **71b** as a colorless oil, 0.27 g (73%).

$\mathbf{R}_f$ 0.31 (hexane/ethyl acetate, 4:1);

$[\alpha]^{26}_D = +18°$ ($c = 4.1$, $CHCl_3$);

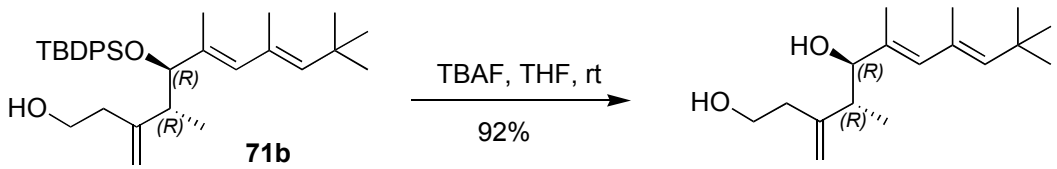
^{1}H NMR (500 MHz, $CDCl_3$): δ 0.84 (3H, d, *J* = 7.4 Hz, -CH-C**H**$_3$), 1.08 (9H, s, -C(C**H**$_3$)$_3$), 1.14 (9H, s, -C-(C**H**$_3$)$_3$), 1.63 (3H, d, *J* = 1.4 Hz, -C-C**H**$_3$), 1.65 (3H, d, *J* = 0.9 Hz, -C-C**H**$_3$), 2.06 (1H, dt, *J* = 14.75, 5.55 Hz, -C**H**$_2$-CH$_2$-OH), 2.21 (1H, dt, *J* = 14.75, 6.95 Hz, -C**H**$_2$-CH$_2$-OH), 2.43 (1H, dq, *J* = 8.3, 7.4 Hz, -C**H**-CH$_3$), 3.61 (2H, td, *J* = 7.15, 1.4 Hz, -C**H**$_2$-OH), 4.00 (1H, d, *J* = 8.3 Hz, -C**H**-OTBDPS), 4.81 (1H, d, *J* = 1.4 Hz, -C=C**H**$_2$-), 4.89 (1H, s, -C=C**H**-), 5.06 (1H, t, *J* = 1.4 Hz, -C=C**H**$_2$), 5.46 (1H, s, -C=C**H**-), 7.32-7.43 (6H, m, -Ph-**H**), 7.64-7.72 (4H, m, -Ph-**H**) ppm;

^{13}C NMR (125 MHz, $CDCl_3$): δ 13.3 (-**C**H$_3$), 16.8 (-**C**H$_3$), 17.6 (-**C**H$_3$), 19.4 (-**C**(CH$_3$)$_3$), 27.1 (-C(**C**H$_3$)$_3$), 30.9 (-C(**C**H$_3$)$_3$), 32.4 (-**C**(CH$_3$)$_3$), 38.2 (-**C**H$_2$CH$_2$OH), 44.7 (-**C**HCH$_3$), 60.6 (-**C**H$_2$OH), 83.2 (-**C**HOTBDPS), 111.8 (-C=**C**H$_2$), 127.0 (-Ph-**C** x2), 127.2 (-Ph-**C** x2), 129.2 (-Ph-**C**), 129.3 (-Ph-**C**), 130.6 (-**C**=C-), 133.8 (-**C**=C-), 134.1 (-C=**C**H-), 134.2 (-Ph-**C***q*), 134.2 (-Ph-**C***q*), 136.2 (-Ph-**C** x2), 136.3 (-Ph-**C** x2), 139.7 (-C=**C**H-), 148.5 (-**C**=CH$_2$) ppm;

IR (neat cm^{-1}): 3436, 2935, 2843, 1638, 1457;

HRMS (EI) m/z (M^+): obsd 504.3408, calcd 504.3424 for $C_{33}H_{48}O_2Si$.

***Anti*-(4*R*,5*R*,6*E*,8*E*)-4,6,8,10,10-pentamethyl-3-methyleneundeca-6,8-diene-1,5-diol (73b)**



73b $[\alpha]^{27}_{D}$ = -52° (*c* = 4.7, $CHCl_3$)

Follow the standard desilylation of the TBDPS protecting group with TBAF in THF, **73b** was obtained as a colourless oil in 92% yield.

R_f 0.39 (hexane/ethyl acetate, 2:1);

$[\alpha]^{27}_{D}$ = -52° (*c* = 4.7, $CHCl_3$);

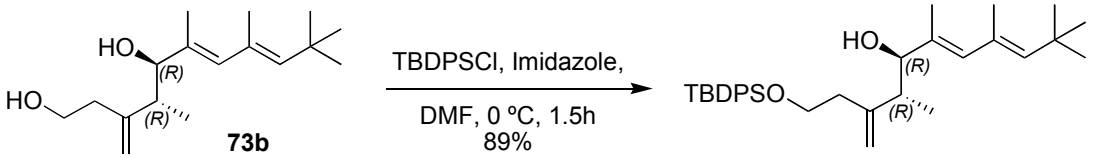
^{1}H NMR (300 MHz, $CDCl_3$): δ 0.85 (3H, d, *J* = 7.32 Hz, -CH-C**H**$_3$), 1.12 (9H, s, -C(C**H**$_3$)$_3$), 1.71 (3H, s, -C-C**H**$_3$), 1.79 (3H, s, -C-C**H**$_3$), 2.22-2.38 (2H, m, -C**H**$_2$-CH_2OH), 2.39 (1H, dq, *J* = 10.08, 7.32 Hz, -C**H**-CH_3), 2.51 (1H, brs, -O**H**), 3.00 (1H, brs, -O**H**), 3.69-3.80 (2H, m, -C**H**$_2$-OH), 3.83 (1H, d, *J* = 10.08 Hz, -C**H**-OH), 4.99 (1H, s, -C=C**H**$_2$-), 5.04 (1H, s, -C=C**H**$_2$), 5.29 (1H, s, -C=C**H**-), 5.81 (1H, s, -C=C**H**-) ppm;

^{13}C NMR (75 MHz, $CDCl_3$): δ 11.8 (-**C**H_3), 17.5 (-**C**H_3), 17.8 (-**C**H_3), 30.8 (-C(**C**H_3)$_3$), 32.5 (-**C**$(CH_3)_3$), 37.0 (-**C**H_2CH_2OH), 43.4 (-**C**HCH_3), 60.8 (-**C**H_2OH), 82.0 (-**C**HOH), 112.9 (-C=**C**H_2), 130.6 (-**C**=CH), 134.1 (-**C**=CH), 134.6 (-C=**C**H), 140.5 (-C=**C**H), 149.2 (-**C**=CH_2) ppm;

IR (neat, cm^{-1}): 3364, 2958, 2863, 2384, 2349, 1641, 1459, 1442;

HRMS (EI) m/z (M^+): obsd 266.2244, calcd 266.2246 for $C_{17}H_{30}O_2$.

***Anti*-(4*R*,5*R*,6*E*,8*E*)-1-(*tert*-butyldiphenylsilyloxy)-4,6,8,10,10-pentamethyl-3-methyleneundeca-6,8-dien-5-ol (34b)**



34b $[\alpha]^{27}_{D}$ = -18° (c = 11.1, $CHCl_3$)

Follow the standard procedure for TBDPS protection with TBDPSCl and imidazole in DMF, **34b** was obtained as a colourless oil in 89% yield.

$\mathbf{R}_f$ 0.78 (hexane/ethyl acetate, 4:1);

$[\alpha]^{27}_{D}$ = -18° (*c* = 11.1, $CHCl_3$);

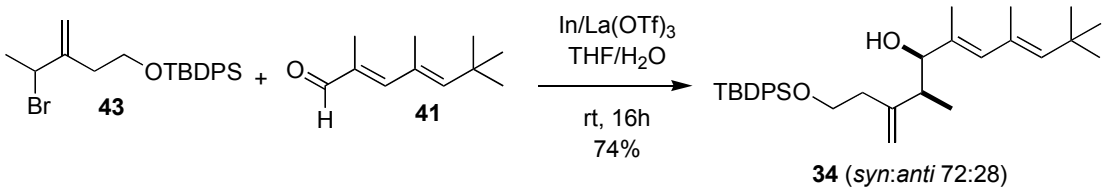
^{1}H NMR (500 MHz, $CDCl_3$): δ 0.83 (3H, d, *J* = 6.95 Hz, -CH-C**H**$_3$), 1.05 (9H, s, -C(C**H**$_3$)$_3$), 1.15 (9H, s, -C-(C**H**$_3$)$_3$), 1.72 (3H, d, *J* = 1.4 Hz, -C-C**H**$_3$), 1.82 (3H, d, *J* = 1.4 Hz, -C-C**H**$_3$), 2.23-2.30 (2H, m, -C**H**$_2$-C-), 2.33 (1H, dq, *J* = 9.70, 6.95 Hz, -C**H**-CH$_3$), 3.74 (1H, d, *J* = 9.70 Hz, -C**H**-OH), 3.77-3.86 (2H, m, -C**H**$_2$OTBDPS), 4.94 (1H, s, -C=C**H**-), 5.01 (1H, s, -C=C**H**$_2$), 5.32 (1H, s, -C=C**H**$_2$-), 5.81 (1H, s, -C=C**H**-), 7.37-7.43 (6H, m, -Ph-**H**), 7.68-7.70 (4H, m, -Ph-**H**) ppm;

^{13}C NMR (75 MHz, $CDCl_3$): δ 12.0 (-**C**H$_3$), 16.9 (-**C**H$_3$), 18.0 (-**C**H$_3$), 19.2 (-**C**(CH$_3$)$_3$), 26.9 (-C(**C**H$_3$)$_3$), 31.0 (-C(**C**H$_3$)$_3$), 32.6 (-**C**(CH$_3$)$_3$), 36.2 (-**C**H$_2$CH$_2$OTBDPS), 44.9 (-**C**H-CH$_3$), 62.9 (-**C**H$_2$OTBDPS), 81.0 (-**C**HOH), 113.3 (-C=**C**H$_2$), 127.7 (-Ph-**C** x4), 129.7 (-Ph-**C** x2), 130.8 (-**C**=CH-), 133.8 (-**C**=CH-), 133.9 (-Ph-C*q* x2), 134.5 (-C=**C**H-), 135.6 (-Ph-**C** x4), 140.3 (-C=**C**H-), 148.6 (-**C**=CH$_2$) ppm;

IR (neat, cm^{-1}): 3426, 3073, 3051, 2960, 2931, 1639, 1462, 1428;

HRMS (EI) m/z (M^+): obsd 504.3420, calcd 504.3424 for $C_{33}H_{48}SiO_2$.

Syn-(6*E*,8*E*)-1-(*tert*-butyldiphenylsilyloxy)-4,6,8,10,10-pentamethyl-3-methyleneundeca-6,8-dien-5-ol (34)



To a stirred solution of **43** (1.25 g, 3 mmol) in THF/H_2O (1:1) (10 mL) was added indium (0.52 g, 4.5 mmol). After vigorous stirring for 30 minutes at room temperature, La(OTf)$_3$ (1.76 g, 3 mmol) and **41** (0.5 g, 3 mmol) were added. The mixture was stirred vigorously at room temperature for 16h. After the reaction was completed (monitored by TLC), the reaction mixture was extracted with ethyl acetate. The organic extracts were combined and washed with *sat*. $NaHCO_3$ solution, brine, dried over anhydrous Na_2SO_4, and concentrated in *vacuo*. The crude product was purified by flash chromatography on silica gel, eluting with 1% ethyl acetate in hexane resulted **34** as a colorless oil (1.12 g, 74%), *syn*/*anti* isomer is in the ratio of 72:28.

R_f 0.75 (hexane/ethyl acetate, 4:1);

^{1}H NMR (300 MHz, $CDCl_3$): δ 0.95 (3H, d, *J* = 6.96 Hz, -CH-C**H**$_3$), 1.05 (9H, s, -C(C**H**$_3$)$_3$), 1.14 (9H, s, -C(C**H**$_3$)$_3$), 1.65 (3H, d, *J* = 1.05 Hz, -C-C**H**$_3$), 1.78 (3H, d, *J* = 1.05 Hz, -C-C**H**$_3$), 2.28-2.42 (3H, m, -C**H**$_2$CH$_2$OTBDPS, -C**H**-CH$_3$), 3.78 (2H, t, *J* = 6.96 Hz, -C**H**$_2$OTBDPS), 3.94 (1H, d, *J* = 4.89 Hz, -C**H**-OH), 4.88 (1H, d, *J* = 1.05 Hz, -C=C**H**$_2$-), 4.90 (1H, d, *J* = 1.05 Hz, -C=C**H**$_2$), 5.25 (1H, t, *J* = 1.05 Hz, -C=C**H**-), 5.86 (1H, s, -C=C**H**-), 7.36-7.43 (6H, m, -Ph-**H**), 7.66-7.69 (4H, m, -Ph-**H**) ppm;

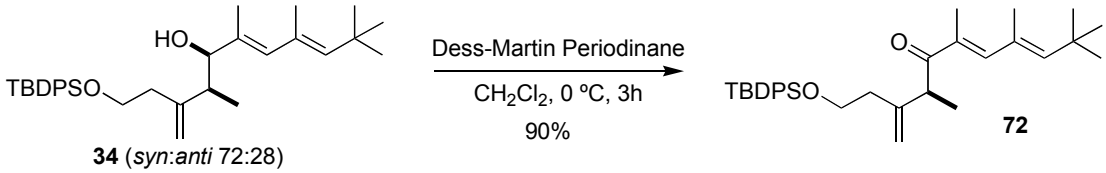
^{13}C NMR (75 MHz, $CDCl_3$): δ 13.0 (-**C**H$_3$), 14.4 (-**C**H$_3$), 18.1 (-**C**H$_3$), 19.2 (-**C**(CH$_3$)$_3$), 26.9 (-C(**C**H$_3$)$_3$), 31.0 (-C(**C**H$_3$)$_3$), 32.6 (-**C**(CH$_3$)$_3$), 37.8 (-**C**H$_2$CH$_2$OTBDPS), 43.1 (-**C**H-CH$_3$), 63.4 (-**C**H$_2$OTBDPS), 81.0 (-**C**HOH), 112.1 (-C=**C**H$_2$), 127.7 (-Ph-**C** x4), 129.6 (-Ph-**C** x2), 131.1 (-**C**=CH-), 131.3 (-C=**C**H-),

133.8 (-**C**=CH-), 134.1 (-Ph-C*q*), 135.6 (-Ph-**C** x4), 139.8 (-C=**C**H-), 149.0 (-**C**=CH_2) ppm;

IR (neat, cm^{-1}): 3466, 3073, 2958, 2860, 1742, 1641, 1469, 1428;

HRMS (EI) m/z (M^+): obsd 504.3408, calcd 504.3424 for $C_{33}H_{48}SiO_2$.

(6*E*,8*E*)-1-(*tert*-butyldiphenylsilyloxy)-4,6,8,10,10-pentamethyl-3-methyleneundeca-6,8-dien-5-one (72)



34 (*syn*:*anti* 72:28)

To a solution of Dess-Martin reagent (1.39 g, 3.27 mmol) in anhydrous CH_2Cl_2 (10 mL) was added dropwise of **34** (1.1 g, 2.18 mmol) prediluted in CH_2Cl_2 (5 mL) at 0 °C. The reaction mixture was stirred under nitrogen at 0 °C for 3h. After completion, the reaction mixture was diluted with ether and poured slowly into a $Na_2S_2O_3$: $NaHCO_3$ (1:1) solution and stirred for 10 minutes and extract with ether. The combine etherate layer was washed with $NaHCO_3$, brine and dried over anhydrous $MgSO_4$. Solvent was removed by concentration in *vacuo*. The residue was purified by flash chromatography on silica gel to provide **72** as a colorless oil, 0.99 g (90%).

R_f 0.85 (hexane/ethyl acetate; 4:1);

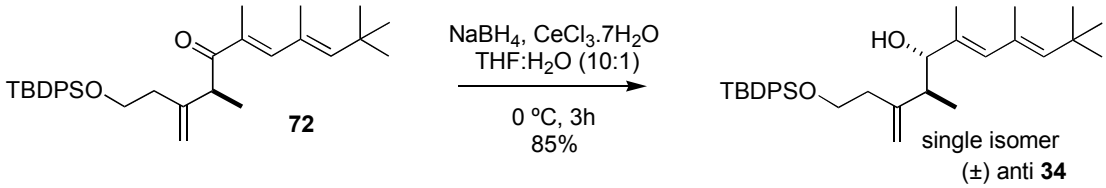
^{1}H NMR (300 MHz, $CDCl_3$): δ 1.04 (9H, s, -C(C**H**$_3$)$_3$), 1.16 (9H, s, -C(C**H**$_3$)$_3$), 1.19 (3H, d, *J* = 6.96 Hz, -CH-C**H**$_3$), 1.87 (3H, d, *J* = 1.05 Hz, -C-C**H**$_3$), 1.88 (3H, d, *J* = 1.41 Hz, -C-C**H**$_3$), 2.23 (1H, dt, *J* = 14.64, 6.96 Hz, -C**H**$_2$CH$_2$OTBDPS), 2.34 (1H, dt, *J* = 14.64, 6.96 Hz, -C**H**$_2$CH$_2$OTBDPS), 3.77 (2H, t, *J* = 6.96 Hz, -C**H**$_2$OTBDPS), 3.89 (1H, q, *J* = 6.96 Hz, -C**H**-CH$_3$), 4.87 (2H, s, -C=C**H**$_2$), 5.52 (1H, s, -C=C**H**-), 6.92 (1H, s, -C=C**H**-), 7.35-7.45 (6H, m, -Ph-**H**), 7.65-7.68 (4H, m, -Ph-**H**) ppm;

^{13}C NMR (75 MHz, $CDCl_3$): δ 13.5 (-**C**H_3), 17.0 (-**C**H_3), 17.5 (-**C**H_3), 19.2 (-**C**$(CH_3)_3$), 26.9 (-C(**C**$H_3)_3$), 30.7 (-C(**C**$H_3)_3$), 33.1 (-**C**$(CH_3)_3$), 37.6 (-**C**H_2CH_2OTBDPS), 46.8 (-**C**H-CH_3), 63.1 (-**C**H_2OTBDPS), 112.8 (-C=**C**H_2), 127.7 (-Ph-**C** x4), 129.6 (-Ph-**C** x2), 131.0 (-**C**=CH-), 133.9 (-Ph-C*q* x2), 134.0 (-C=**C**H-), 135.6 (-Ph-**C** x4), 144.8 (-C=**C**H-), 145.3 (-**C**=CH-), 146.8 (-**C**=CH_2), 203.5 (-**C**=O) ppm;

IR (neat, cm^{-1}): 3067, 3051, 2958, 2930, 2858, 1736, 1586, 1429;

HRMS (EI) m/z [M-(C_4H_9)]$^+$: obsd 445.2549, calcd 445.2563 for $C_{29}H_{37}SiO_2$.

***Anti*-(6*E*,8*E*)-1-(*tert*-butyldiphenylsilyloxy)-4,6,8,10,10-pentamethyl-3-methyleneundeca-6,8-dien-5-ol (34)**



To a solution of **72** (1.1 g, 2.2 mmol) in THF:H_2O (10:1) (10 mL) was added in $CeCl_3.7H_2O$ (1.64 g, 4.4 mmol) at 0 °C. After the mixture was stirred at 0 °C for 15 minutes, $NaBH_4$ (0.16 g, 4.4 mmol) was added and the reaction was stirred for 3h. After the reaction was completed (monitored by TLC), THF was removed under *vacuo*. H_2O was added in and the mixture was extracted with ether. The combined etherate layer was washed with brine, dried over $MgSO_4$, concentrated and purified through flash chromatography on silica gel to afford *anti* **34** as a colorless oil, 0.94 g (85%). (*anti:syn* > 99:1)

R_f 0.78 (hexane/ethyl acetate, 4:1);

^{1}H NMR (500 MHz, $CDCl_3$): δ 0.83 (3H, d, *J* = 6.95 Hz, -CH-C**H**$_3$), 1.05 (9H, s, -C(C**H**$_3)_3$), 1.15 (9H, s, -C-(C**H**$_3)_3$), 1.72 (3H, d, *J* = 1.4 Hz, -C-C**H**$_3$), 1.82 (3H, d, *J* = 1.4 Hz, -C-C**H**$_3$), 2.23-2.30 (2H, m, -C**H**$_2$-C-), 2.33 (1H, dq, *J* = 9.70, 6.95 Hz, -C**H**-

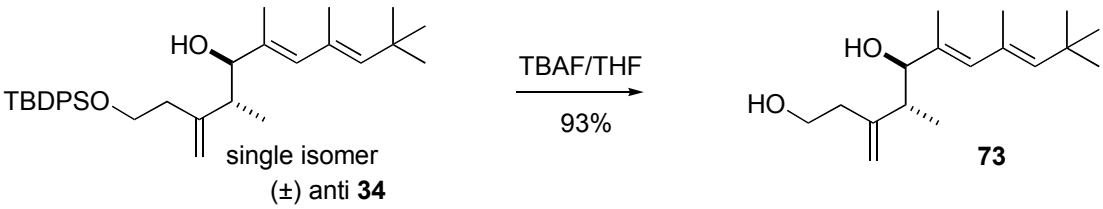
CH_3), 3.74 (1H, d, *J* = 9.70 Hz, -C**H**-OH), 3.77-3.86 (2H, m, -C**H**$_2$OTBDPS), 4.94 (1H, s, -C=C**H**-), 5.01 (1H, s, -C=C**H**$_2$), 5.32 (1H, s, -C=C**H**$_2$-), 5.81 (1H, s, -C=C**H**-), 7.37-7.43 (6H, m, -Ph-**H**), 7.68-7.70 (4H, m, -Ph-**H**) ppm;

^{13}C NMR (75 MHz, $CDCl_3$): δ 12.0 (-**C**H_3), 16.9 (-**C**H_3), 18.0 (-**C**H_3), 19.2 (-**C**$(CH_3)_3$), 26.9 (-C(**C**$H_3)_3$), 31.0 (-C(**C**$H_3)_3$), 32.6 (-**C**$(CH_3)_3$), 36.2 (-**C**H_2CH_2OTBDPS), 44.9 (-**C**H-CH_3), 62.9 (-**C**H_2OTBDPS), 81.0 (-**C**HOH), 113.3 (-C=**C**H_2), 127.7 (-Ph-**C** x4), 129.7 (-Ph-**C** x2), 130.8 (-**C**=CH-), 133.8 (-**C**=CH-), 133.9 (-Ph-C*q* x2), 134.5 (-C=**C**H-), 135.6 (-Ph-**C** x4), 140.3 (-C=**C**H-), 148.6 (-**C**=CH_2) ppm;

IR (neat, cm^{-1}): 3426, 3073, 3051, 2960, 2931, 1639, 1462, 1428;

HRMS (EI) m/z (M^+): obsd 504.3420, calcd 504.3424 for $C_{33}H_{48}SiO_2$.

***Anti*-(6*E*,8*E*)-4,6,8,10,10-pentamethyl-3-methyleneundeca-6,8-diene-1,5-diol (73)**



Follow the standard desilylation procedure using TBAF in THF afforded *anti* **73** as colourless oil in 93% yield.

R_f 0.39 (hexane/ethyl acetate, 2:1);

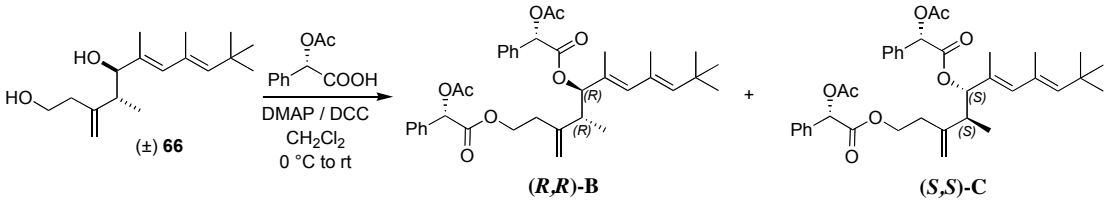
^{1}H NMR (300 MHz, $CDCl_3$): δ 0.85 (3H, d, *J* = 7.32 Hz, -CH-C**H**$_3$), 1.12 (9H, s, -C(C**H**$_3)_3$), 1.71 (3H, s, -C-C**H**$_3$), 1.79 (3H, s, -C-C**H**$_3$), 2.22-2.38 (2H, m, -C**H**$_2$-CH_2OH), 2.39 (1H, dq, *J* = 10.08, 7.32 Hz, -C**H**-CH_3), 2.51 (1H, brs, -O**H**), 3.00 (1H, brs, -O**H**), 3.69-3.80 (2H, m, -C**H**$_2$-OH), 3.83 (1H, d, *J* = 10.08 Hz, -C**H**-OH), 4.99 (1H, s, -C=C**H**$_2$-), 5.04 (1H, s, -C=C**H**$_2$), 5.29 (1H, s, -C=C**H**-), 5.81 (1H, s, -C=C**H**-) ppm;

^{13}C NMR (75 MHz, $CDCl_3$): δ 11.8 (-**C**H_3), 17.5 (-**C**H_3), 17.8 (-**C**H_3), 30.8 (-C(**C**H_3)$_3$), 32.5 (-**C**(CH$_3$)$_3$), 37.0 (-**C**H_2CH$_2$OH), 43.4 (-**C**HCH$_3$), 60.8 (-**C**H_2OH), 82.0 (-**C**HOH), 112.9 (-C=**C**H_2), 130.6 (-**C**=CH), 134.1 (-**C**=CH), 134.6 (-C=**C**H), 140.5 (-C=**C**H), 149.2 (-**C**=CH$_2$) ppm;

IR (neat, cm^{-1}): 3364, 2958, 2863, 2384, 2349, 1641, 1459, 1442;

HRMS (EI) m/z (M$^+$): obsd 266.2244, calcd 266.2246 for $C_{17}H_{30}O_2$.

***Anti*-(1*S*,1'*S*)-2,2'-((4*R*,5*R*,6*E*,8*E*)-4,6,8,10,10-pentamethyl-3-methyleneundeca-6,8-diene-1,5-diyl)bis(oxy)bis(2-oxo-1-phenylethane-2,1-diyl) diacetate (*R,R*)-B and *Anti*-(1*S*,1'*S*)-2,2'-((4*S*,5*S*,6*E*,8*E*)-4,6,8,10,10-pentamethyl-3-methyleneundeca-6,8-diene-1,5-diyl)bis(oxy)bis(2-oxo-1-phenylethane-2,1-diyl) diacetate (*S,S*)-C**



To a mixture of *anti* (±)-**66** (0.19 g, 0.71 mmol), *S*-(+)-α-acetoxyphenylacetic acid (0.42 g, 2.13 mmol) and DMAP (9 mg, 0.071 mmol) in dried CH_2Cl_2 (3 mL) was added in DCC (0.37 g, 1.77 mmol) prediluted in 1 mL CH_2Cl_2 dropwise at 0 °C. The reaction mixture was stirred at 0 °C to room temperature for 12h. After completion, CH_2Cl_2 was removed *via* rotary evaporator and the crude product was directly subjected to column chromatography. Purification by flash chromatography on silica gel (Hex:CH_2Cl_2:EA, 3:3:0.2) afforded two pure enantiomer as colorless oil with 97% overall yield.

(*R,R*)-B

R$_f$ 0.37 (hexane/CH_2Cl_2/ethyl acetate, 3:3:0.2);

^{1}H NMR (300 MHz, $CDCl_3$): δ 0.76 (3H, d, *J* = 7.29 Hz, -CH-C**H**$_3$), 1.14 (9H, s, -C(C**H**$_3$)$_3$), 1.70 (3H, d, *J* = 1.05 Hz, -C-C**H**$_3$), 1.78 (3H, d, *J* = 1.05 Hz, -C-C**H**$_3$), 2.13 (3H, s, -O**Ac**), 2.19 (3H, s, -O**Ac**), 2.23-2.40 (3H, m, -C**H**$_2$CH$_2$O-, -C**H**-CH$_3$), 3.82 (1H, dt, *J* = 10.44, 7.65 Hz, -CH$_2$C**H**$_2$O-), 3.97 (1H, dt, *J* = 10.44, 7.32 Hz, -CH$_2$C**H**$_2$O-), 4.34 (1H, s, -C=C**H**$_2$-), 4.57 (1H, s, -C=C**H**$_2$), 4.97 (1H, d, *J* = 10.08 Hz, -C**H**-O-), 5.27 (1H, s, -C=C**H**-), 5.85 (1H, s, -C**H**-OAc), 5.88 (1H, s, -C**H**-OAc), 5.89 (1H, s, -C=C**H**-), 7.26-7.28 (3H, m, -Ph-**H**), 7.35-7.40 (5H, m, -Ph-**H**), 7.45-7.47 (2H, m, -Ph-**H**) ppm;

^{13}C NMR (75 MHz, $CDCl_3$): δ 12.8 (-**C**H$_3$), 16.8 (-**C**H$_3$), 17.7 (-**C**H$_3$), 20.6 (-**C**H$_3$), 30.8 (-C(**C**H$_3$)$_3$), 32.1 (-**C**H$_2$CH$_2$O-), 32.5 (-**C**(CH$_3$)$_3$), 42.0 (-**C**H-CH$_3$), 63.9 (-**C**H$_2$O-), 74.4 (-**C**H-OAc), 74.5 (-**C**H-OAc), 84.1 (-**C**H-O-), 111.8 (-C=**C**H$_2$), 127.6 (-Ph-C*m* x2), 127.8 (-Ph-C*m* x2), 128.5 (-Ph-C*o* x2), 128.7 (-Ph-C*o* x2), 129.0 (-Ph-C*p*), 129.1 (-Ph-C*p*), 129.6 (-HC=**C**-CH$_3$), 130.4 (-HC=**C**-CH$_3$), 133.7 (-Ph-C*q*), 134.1 (-Ph-C*q*), 136.4 (-**C**H=C-CH$_3$), 140.8 (-**C**H=C-CH$_3$), 145.6 (-**C**=CH$_2$), 167.6 (**C**=O), 168.6 (**C**=O), 169.9 (**C**=O), 170.2 (**C**=O) ppm;

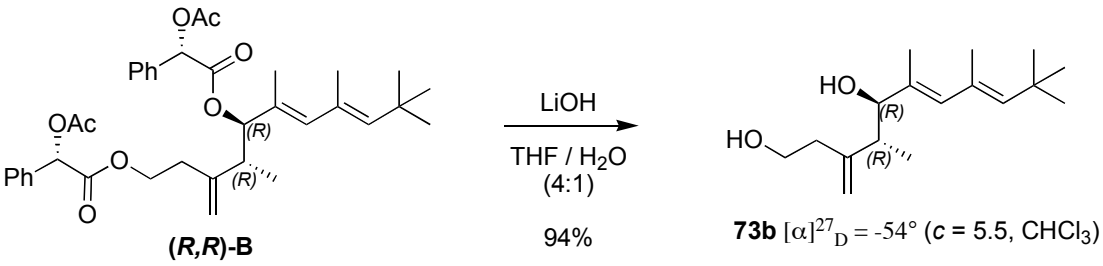
(*S*,*S*)-C

R$_f$ 0.26 (hexane/CH_2Cl_2/ethyl acetate, 3:3:0.2);

^{1}H NMR (300 MHz, $CDCl_3$): δ 0.85 (3H, d, *J* = 7.32 Hz, -CH-C**H**$_3$), 1.12 (9H, s, -C(C**H**$_3$)$_3$), 1.36 (3H, d, *J* = 1.05 Hz, -C-C**H**$_3$), 1.68 (3H, d, *J* = 1.05 Hz, -C-C**H**$_3$), 2.16 (3H, s, -O**Ac**), 2.20 (3H, s, -O**Ac**), 2.40-2.71 (3H, m, -C**H**$_2$CH$_2$O-, -C**H**-CH$_3$), 4.21-4.30 (2H, m, -C**H**$_2$-O-), 4.75 (1H, s, -C=C**H**$_2$-), 4.88 (1H, s, -C=C**H**$_2$), 5.02 (1H, d, *J* = 10.11 Hz, -C**H**-O-), 5.11 (1H, s, -C=C**H**-), 5.73 (1H, s, -C=C**H**-), 5.89 (1H, s, -C**H**-OAc), 5.96 (1H, s, -C**H**-OAc), 7.33-7.41 (6H, m, -Ph-**H**), 7.49-7.52 (4H, m, -Ph-**H**) ppm;

^{13}C NMR (125 MHz, $CDCl_3$): δ 12.3 (-**C**H_3), 16.8 (-**C**H_3), 17.5 (-**C**H_3), 20.5 (-**C**H_3), 30.7 (-C(**C**H_3)$_3$), 32.4 (-**C**(CH$_3$)$_3$), 33.3 (-**C**H_2CH$_2$O-), 41.3 (-**C**H-CH$_3$), 63.9 (-**C**H_2O-), 74.2 (-**C**H-OAc), 74.4 (-**C**H-OAc), 84.3 (-**C**H-O-), 112.3 (-C=**C**H_2), 127.5 (-Ph-**C***m* x2), 127.6 (-Ph-**C***m* x2), 128.4 (-Ph-**C***o* x2), 128.6 (-Ph-**C***o* x2), 128.9 (-Ph-**C***p*), 129.0 (-Ph-**C***p*), 129.4, (-HC=**C**-CH$_3$), 130.2 (-HC=**C**-CH$_3$), 133.8 (-Ph-**C***q*), 133.9 (-Ph-**C***q*), 136.2 (-**C**H=C-CH$_3$), 140.5 (-**C**H=C-CH$_3$), 145.9 (-**C**=CH$_2$), 167.6 (**C**=O), 168.7 (**C**=O), 169.8 (**C**=O), 170.1 (**C**=O) ppm;

***Anti*-(4*R*,5*R*,6*E*,8*E*)-4,6,8,10,10-pentamethyl-3-methyleneundeca-6,8-diene-1,5-diol (73b)**



Follow the standard hydrolysis procedure, **73b** was obtained as a colourless oil in 94% yield.

R$_f$ 0.39 (hexane/ethyl acetate, 2:1);

$[\alpha]^{27}_D$ = -54° (*c* = 5.5, $CHCl_3$);

^{1}H NMR (300 MHz, $CDCl_3$): δ 0.85 (3H, d, *J* = 7.32 Hz, -CH-C**H**$_3$), 1.12 (9H, s, -C(C**H**$_3$)$_3$), 1.71 (3H, s, -C-C**H**$_3$), 1.79 (3H, s, -C-C**H**$_3$), 2.22-2.38 (2H, m, -C**H**$_2$-CH$_2$OH), 2.39 (1H, dq, *J* = 10.08, 7.32 Hz, -C**H**-CH$_3$), 2.51 (1H, brs, -O**H**), 3.00 (1H, brs, -O**H**), 3.69-3.80 (2H, m, -C**H**$_2$-OH), 3.83 (1H, d, *J* = 10.08 Hz, -C**H**-OH), 4.99 (1H, s, -C=C**H**$_2$-), 5.04 (1H, s, -C=C**H**$_2$), 5.29 (1H, s, -C=C**H**-), 5.81 (1H, s, -C=C**H**-) ppm;

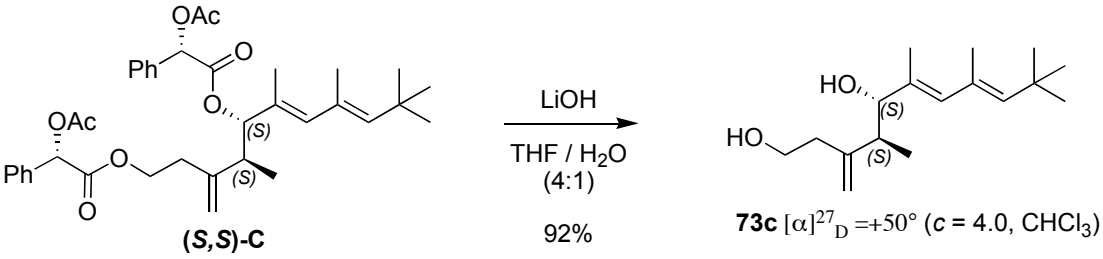
^{13}C NMR (75 MHz, $CDCl_3$): δ 11.8 (-**C**H_3), 17.5 (-**C**H_3), 17.8 (-**C**H_3), 30.8 (-C(**C**H_3)$_3$), 32.5 (-**C**(CH$_3$)$_3$), 37.0 (-**C**H_2CH$_2$OH), 43.4 (-**C**HCH$_3$), 60.8 (-**C**H_2OH), 82.0

(-**C**HOH), 112.9 (-C=**C**H_2), 130.6 (-**C**=CH), 134.1 (-**C**=CH), 134.6 (-C=**C**H), 140.5 (-C=**C**H), 149.2 (-**C**=CH_2) ppm;

IR (neat, cm^{-1}): 3364, 2958, 2863, 2384, 2349, 1641, 1459, 1442;

HRMS (EI) m/z (M^+): obsd 266.2244, calcd 266.2246 for $C_{17}H_{30}O_2$.

***Anti*-(4*S*,5*S*,6*E*,8*E*)-4,6,8,10,10-pentamethyl-3-methyleneundeca-6,8-diene-1,5-diol (73c)**



Follow the standard hydrolysis procedure, **73c** was obtained as a colourless oil in 92% yield.

R_f 0.39 (hexane/ethyl acetate, 2:1);

$[\alpha]^{26}_D$ = +50° (*c* = 4.0, $CHCl_3$);

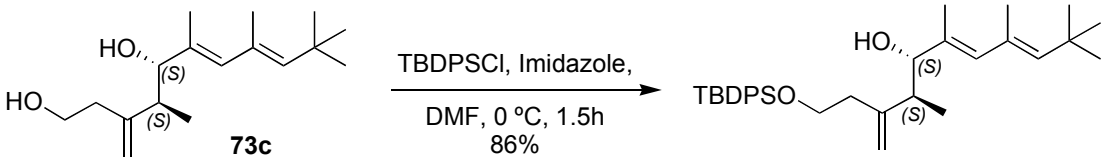
^{1}H NMR (300 MHz, $CDCl_3$): δ 0.85 (3H, d, *J* = 7.32 Hz, -CH-C**H**$_3$), 1.12 (9H, s, -C(C**H**$_3$)$_3$), 1.71 (3H, s, -C-C**H**$_3$), 1.79 (3H, s, -C-C**H**$_3$), 2.22-2.38 (2H, m, -C**H**$_2$-CH_2OH), 2.39 (1H, dq, *J* = 10.08, 7.32 Hz, -C**H**-CH_3), 2.51 (1H, brs, -O**H**), 3.00 (1H, brs, -O**H**), 3.69-3.80 (2H, m, -C**H**$_2$-OH), 3.83 (1H, d, *J* = 10.08 Hz, -C**H**-OH), 4.99 (1H, s, -C=C**H**$_2$-), 5.04 (1H, s, -C=C**H**$_2$), 5.29 (1H, s, -C=C**H**-), 5.81 (1H, s, -C=C**H**-) ppm;

^{13}C NMR (75 MHz, $CDCl_3$): δ 11.8 (-**C**H_3), 17.5 (-**C**H_3), 17.8 (-**C**H_3), 30.8 (-C(**C**H_3)$_3$), 32.5 (-**C**$(CH_3)_3$), 37.0 (-**C**H_2CH_2OH), 43.4 (-**C**HCH_3), 60.8 (-**C**H_2OH), 82.0 (-**C**HOH), 112.9 (-C=**C**H_2), 130.6 (-**C**=CH), 134.1 (-**C**=CH), 134.6 (-C=**C**H), 140.5 (-C=**C**H), 149.2 (-**C**=CH_2) ppm;

IR (neat, cm^{-1}): 3364, 2958, 2863, 2384, 2349, 1641, 1459, 1442;

HRMS (EI) m/z (M^+): obsd 266.2244, calcd 266.2246 for $C_{17}H_{30}O_2$.

***Anti*-(4*S*,5*S*,6*E*,8*E*)-1-(*tert*-butyldiphenylsilyloxy)-4,6,8,10,10-pentamethyl-3-methyleneundeca-6,8-dien-5-ol (34c)**



34c $[\alpha]^{27}_D$ = +15° (*c* = 9.0, $CHCl_3$)

Follow the standard TBDPS protection using TBDPSCl and imidazole in DMF, **34c** was obtained as a colourless oil in 86% yield.

$\mathbf{R}_f$ 0.78 (hexane/ethyl acetate, 4:1);

$[\alpha]^{27}_D$ = +15° (*c* = 9.0, $CHCl_3$);

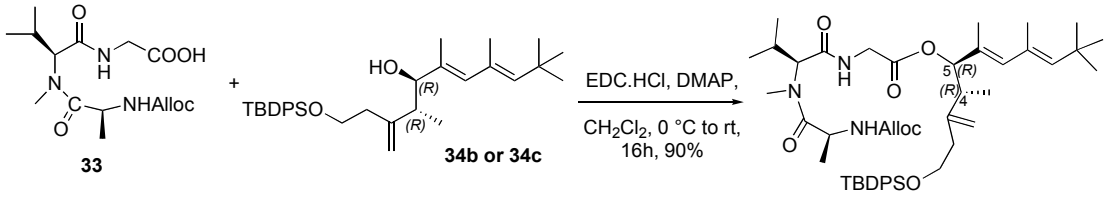
^{1}H NMR (500 MHz, $CDCl_3$): δ 0.83 (3H, d, *J* = 6.95 Hz, -CH-C**H**$_3$), 1.05 (9H, s, -C(C**H**$_3$)$_3$), 1.15 (9H, s, -C-(C**H**$_3$)$_3$), 1.72 (3H, d, *J* = 1.4 Hz, -C-C**H**$_3$), 1.82 (3H, d, *J* = 1.4 Hz, -C-C**H**$_3$), 2.23-2.30 (2H, m, -C**H**$_2$-C-), 2.33 (1H, dq, *J* = 9.70, 6.95 Hz, -C**H**-CH$_3$), 3.74 (1H, d, *J* = 9.70 Hz, -C**H**-OH), 3.77-3.86 (2H, m, -C**H**$_2$OTBDPS), 4.94 (1H, s, -C=C**H**-), 5.01 (1H, s, -C=C**H**$_2$), 5.32 (1H, s, -C=C**H**$_2$-), 5.81 (1H, s, -C=C**H**-), 7.37-7.43 (6H, m, -Ph-**H**), 7.68-7.70 (4H, m, -Ph-**H**) ppm;

^{13}C NMR (75 MHz, $CDCl_3$): δ 12.0 (-**C**H$_3$), 16.9 (-**C**H$_3$), 18.0 (-**C**H$_3$), 19.2 (-**C**(CH$_3$)$_3$), 26.9 (-C(**C**H$_3$)$_3$), 31.0 (-C(**C**H$_3$)$_3$), 32.6 (-**C**(CH$_3$)$_3$), 36.2 (-**C**H$_2$CH$_2$OTBDPS), 44.9 (-**C**H-CH$_3$), 62.9 (-**C**H$_2$OTBDPS), 81.0 (-**C**HOH), 113.3 (-C=**C**H$_2$), 127.7 (-Ph-**C** x4), 129.7 (-Ph-**C** x2), 130.8 (-**C**=CH-), 133.8 (-**C**=CH-), 133.9 (-Ph-C*q* x2), 134.5 (-C=**C**H-), 135.6 (-Ph-**C** x4), 140.3 (-C=**C**H-), 148.6 (-**C**=CH$_2$) ppm;

IR (neat, cm^{-1}): 3426, 3073, 3051, 2960, 2931, 1639, 1462, 1428;

HRMS (EI) m/z (M^+): obsd 504.3420, calcd 504.3424 for $C_{33}H_{48}SiO_2$.

(5*S*,8*S*)-((4*R*,5*R*,6*E*,8*E*)-1-(*tert*-butyldiphenylsilyloxy)-4,6,8,10,10-pentamethyl-3-methyleneundeca-6,8-dien-5-yl) 5-isopropyl-6,8-dimethyl-4,7,10-trioxo-11-oxa-3,6,9-triazatetradec-13-en-1-oate (74b) and (5*S*,8*S*)-((4*S*,5*S*,6*E*,8*E*)-1-(*tert*-butyldiphenylsilyloxy)-4,6,8,10,10-pentamethyl-3-methyleneundeca-6,8-dien-5-yl) 5-isopropyl-6,8-dimethyl-4,7,10-trioxo-11-oxa-3,6,9-triazatetradec-13-en-1-oate (74c)



74b $[\alpha]^{27}_D$ = -68° (*c* = 1.6, $CHCl_3$), 90%;
74c $[\alpha]^{27}_D$ = -52° (*c* = 0.8, $CHCl_3$), 89%;

The *anti* homoallylic alcohol **34b** (0.8 g, 1.58 mmol) and tripeptide acid **33** (1.36 g, 3.96 mmol) were dissolved in CH_2Cl_2 (3 ml), and EDC.HCl (0.76 g, 3.96 mmol) was added followed by the addition of DMAP (0.097 g, 0.79 mmol) at 0 °C. The mixture was stirred for 12h at room temperature. After completion, monitored by TLC, the reaction mixture was diluted with ether. The combined organic layer was washed with 5% $KHSO_4$, water, saturated $NaHCO_3$, brine and finally dried over anhydrous $MgSO_4$. After filtration, it was concentrated and purified by flash chromatography on silica gel to give **74b** as a colorless oil (1.18 g, 90%).

74b

$\mathbf{R}_f$ 0.15 (hexane/ethyl acetate, 4:1);

$[\alpha]^{27}_D$ = -68º (*c* = 1.6, $CHCl_3$);

^{1}H NMR (500 MHz, $CDCl_3$): δ 0.82 (6H, dd, *J* = 6.95, 0.9 Hz, C_{13}-C**H**$_3$, Val-C**H**$_3$), 0.95 (3H, d, *J* = 6.45 Hz, Val-C**H**$_3$), 1.04 (9H, s, -C(C**H**$_3$)$_3$), 1.13 (9H, s, -C(C**H**$_3$)$_3$), 1.30 (3H, d, *J* = 6.95 Hz, Ala-C**H**$_3$), 1.65 (3H, d, *J* = 1.4 Hz, C_{14}-C**H**$_3$), 1.77 (3H, d, *J* = 1.4 Hz, -C_{15}-C**H**$_3$), 2.24 (1H, d, *J* = 6.95 Hz, C_2-**H**), 2.26 (1H, d, *J* = 6.95 Hz, C_2-**H**), 2.29 (1H, m, C_4-**H**), 2.44 (1H, m, Val-$(CH_3)_2$C**H**), 3.00 (3H, s, N-C**H**$_3$), 3.73 (3H, m, Gly-C**H**$_2$, -C**H**$_2$-O-), 3.86 (1H, dd, *J* = 18.27, 6.00 Hz, Gly-C**H**$_2$), 4.54 (2H, d, *J* = 5.1

Hz, CH_2=CHC**H**$_2$-), 4.62 (1H, d, *J* = 11.05 Hz, Val-α-**H**), 4.66 (1H, dq, *J* = 7.85, 6.95 Hz, Ala-α-**H**), 4.77 (1H, s, C_{12}-**H**), 4.82 (1H, s, C_{12}-**H**), 5.02 (1H, d, *J* = 10.2 Hz, C_5-**H**), 5.19 (1H, dd, *J* = 10.20, 1.35 Hz, C**H**$_2$=CHCH$_2$-), 5.27 (1H, s, C_9-**H**), 5.28 (1H, dd, *J* = 15.95, 1.40 Hz, C**H**$_2$=CHCH$_2$-), 5.76 (1H, d, *J* = 7.85 Hz, Ala-N**H**), 5.86 (1H, s, C_7-**H**), 5.90 (1H, m, CH_2=C**H**CH$_2$-), 6.56 (1H, brs, Gly-N**H**), 7.38 (6H, m, -Ph-**H**), 7.67 (4H, m, -Ph-**H**) ppm;

^{13}C NMR (125 MHz, $CDCl_3$): δ 12.7 (-**C**H$_3$), 16.7 (-**C**H$_3$), 17.7 (-**C**H$_3$), 18.2 (-**C**H$_3$), 18.4 (-**C**H$_3$), 19.1 (-**C**(CH$_3$)$_3$), 19.5 (-**C**H$_3$), 25.4 (-CH-(**C**H$_3$)$_2$), 26.8 (-C(**C**H$_3$)$_3$), 30.3 (-N-**C**H$_3$), 30.8 (-C(**C**H$_3$)$_3$), 32.5 (-**C**(CH$_3$)$_3$), 37.5 (-**C**H$_2$-), 40.7 (-**C**H$_2$-), 42.0 (-**C**H-), 47.1 (-**C**H-), 62.5 (-N-**C**H-), 63.3 (-**C**H$_2$-O-), 65.5 (-**C**H$_2$-O-), 84.1 (-**C**H-O-), 111.8 (-C=**C**H$_2$), 117.5 (-CH=**C**H$_2$), 127.5 (-Ph-**C** x4), 129.5 (-Ph-**C** x2), 129.9 (-**C**=CH-), 130.3 (-**C**=CH-), 132.7 (-**C**H=CH$_2$), 133.8 (-Ph-**C***q* x2), 135.5 (-Ph-**C** x4), 136.4 (-**C**H=C-), 141.0 (-**C**H=C-), 147.6 (-**C**=CH$_2$-), 155.4 (-**C**=O), 168.2 (-**C**=O), 169.8 (-**C**=O), 173.9 (-**C**=O) ppm;

IR (neat, cm^{-1}): 3313, 3073, 2961, 1726, 1689,1640, 1529, 1464, 1428;

HRMS (ESI) m/z (M$^+$+Na): obsd 852.4972, calcd 852.4959 for $C_{48}H_{71}NaN_3O_7Si$.

74c

R$_f$ 0.15 (hexane/ethyl acetate, 4:1);

$[\alpha]^{27}_D$ = -52° (*c* = 0.8, $CHCl_3$);

^{1}H NMR (500 MHz, $CDCl_3$): δ 0.82 (6H, d, *J* = 6.95 Hz, C_{13}-C**H**$_3$, Val-C**H**$_3$), 0.94 (3H, d, *J* = 6.50 Hz, Val-C**H**$_3$), 1.04 (9H, s, -C(C**H**$_3$)$_3$), 1.13 (9H, s, -C(C**H**$_3$)$_3$), 1.31 (3H, d, *J* = 6.95 Hz, Ala-C**H**$_3$), 1.65 (3H, d, *J* = 1.4 Hz, C_{14}-C**H**$_3$), 1.77 (3H, d, *J* = 0.9 Hz, -C_{15}-C**H**$_3$), 2.23 (1H, d, *J* = 6.9 Hz, C_2-**H**), 2.24 (1H, d, *J* = 6.95 Hz, C_2-**H**), 2.28 (1H, m, C_4-**H**), 2.43 (1H, m, Val-(CH$_3$)$_2$C**H**), 3.00 (3H, s, N-C**H**$_3$), 3.66 (1H, dd, *J* =

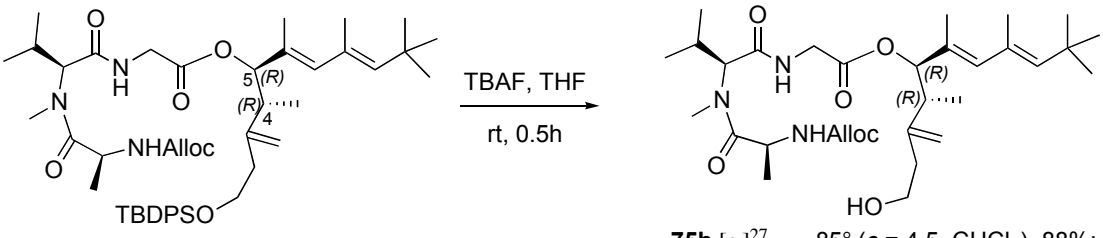
18.02, 4.65 Hz, Gly-C**H**$_2$), 3.74 (2H, m, -C**H**$_2$-O-), 3.94 (1H, dd, *J* = 18.02, 6.05 Hz, Gly-C**H**$_2$), 4.55 (2H, d, *J* = 5.1 Hz, CH_2=CHC**H**$_2$-), 4.61 (1H, d, *J* = 11.10 Hz, Val-α-**H**), 4.66 (1H, dq, *J* = 8.30, 6.95 Hz, Ala-α-**H**), 4.76 (1H, s, C_{12}-**H**), 4.81 (1H, s, C_{12}-**H**), 5.02 (1H, d, *J* = 10.15 Hz, C_5-**H**), 5.19 (1H, dd, *J* = 10.4, 1.4 Hz, C**H**$_2$=CHCH_2-), 5.27 (1H, s, C_9-**H**), 5.29 (1H, dd, *J* = 18.45, 1.85 Hz, C**H**$_2$=CHCH_2-), 5.72 (1H, d, *J* = 8.30 Hz, Ala-N**H**), 5.86 (1H, s, C_7-**H**), 5.90 (1H, m, CH_2=C**H**CH_2-), 6.46 (1H, brs, Gly-N**H**), 7.40 (6H, m, -Ph-**H**), 7.67 (4H, m, -Ph-**H**) ppm;

^{13}C NMR (125 MHz, $CDCl_3$): δ 12.7 (-**C**H_3), 16.8 (-**C**H_3), 17.7 (-**C**H_3), 18.3 (-**C**H_3), 18.4 (-**C**H_3), 19.1 (-**C**$(CH_3)_3$), 19.6 (-**C**H_3), 25.4 (-**C**H-$(CH_3)_2$), 26.8 (-C(**C**$H_3)_3$), 30.4 (-N-**C**H_3), 30.9 (-C(**C**$H_3)_3$), 32.6 (-**C**$(CH_3)_3$), 37.4 (-**C**H_2-), 40.8 (-**C**H_2-), 42.1 (-**C**H-), 47.1 (-**C**H-), 62.5 (-N-**C**H-), 63.3 (-**C**H_2-O-), 65.6 (-**C**H_2-O-), 84.2 (-**C**H-O-), 111.7 (-C=**C**H_2), 117.5 (-CH=**C**H_2), 127.6 (-Ph-**C** x4), 129.6 (-Ph-**C** x2), 129.9 (-**C**=CH-), 130.4 (-**C**=CH-), 132.7 (-**C**H=CH_2), 133.9 (-Ph-**C***q* x2), 135.5 (-Ph-**C** x4), 136.5 (-**C**H=C-), 141.0 (-**C**H=C-), 147.8 (-**C**=CH_2-), 155.4 (-**C**=O), 168.3 (-**C**=O), 169.8 (-**C**=O), 173.9 (-**C**=O) ppm;

IR (neat, cm^{-1}): 3313, 3073, 2961, 1726, 1689,1640, 1529, 1464, 1428;

HRMS (ESI) m/z (M^++Na): obsd 852.4972, calcd 852.4959 for $C_{48}H_{71}NaN_3O_7Si$.

(5*S*,8*S*)-((4*R*,5*R*,6*E*,8*E*)-1-hydroxy-4,6,8,10,10-pentamethyl-3-methyleneundeca-6,8-dien-5-yl) 5-isopropyl-6,8-dimethyl-4,7,10-trioxo-11-oxa-3,6,9-triazatetradec-13-en-1-oate (75b) and (5*S*,8*S*)-((4*S*,5*S*,6*E*,8*E*)-1-hydroxy-4,6,8,10,10-pentamethyl-3-methyleneundeca-6,8-dien-5-yl) 5-isopropyl-6,8-dimethyl-4,7,10-trioxo-11-oxa-3,6,9-triazatetradec-13-en-1-oate (75c)



74b or 74c

75b $[\alpha]^{27}_D$ = -85° (*c* = 4.5, $CHCl_3$), 88%;
75c $[\alpha]^{27}_D$ = -68° (*c* = 2.6, $CHCl_3$), 86%:

To a solution of **74** (0.092 g, 0.11 mmol) in THF (0.5 mL) was added TBAF (0.22 mL, 1.0 M in THF, 0.22 mmol). The mixture was stirred for 30 minutes at room temperature. After the reaction was completed (monitored by TLC), the mixture was concentrated in *vacuo* to remove the THF. The residue was purified by flash chromatography on silica gel to afford **75** as a colorless oil, 0.057 g (88%).

75b

R$_f$ 0.20 (hexane/ethyl acetate, 1:1);

$[\alpha]^{27}_D$ = -85° (*c* = 4.5, $CHCl_3$);

^{1}H NMR (500 MHz, $CDCl_3$): δ 0.80 (3H, d, *J* = 6.50 Hz, Val-C**H**$_3$), 0.88 (3H, d, *J* = 6.95 Hz, C_{13}-C**H**$_3$), 0.92 (3H, d, *J* = 6.45 Hz, Val-C**H**$_3$), 1.10 (9H, s, -C(C**H**$_3$)$_3$), 1.31 (3H, d, *J* = 6.95 Hz, Ala-C**H**$_3$), 1.67 (3H, s, C_{14}-C**H**$_3$), 1.76 (3H, s, -C_{15}-C**H**$_3$), 2.24 (2H, t, *J* = 6.00 Hz, C_2-**H**), 2.22-2.29 (1H, m, Val-$(CH_3)_2$C**H**), 2.49 (1H, dq, *J* = 10.15, 6.95 Hz, C_4-**H**,), 3.00 (3H, s, N-C**H**$_3$), 3.69-3.78 (3H, m, Gly-C**H**$_2$, -C**H**$_2$-OH), 3.98 (1H, dd, *J* = 17.83, 6.00 Hz, Gly-C**H**$_2$), 4.52 (2H, d, *J* = 5.10 Hz, CH_2=CHC**H**$_2$O-), 4.55 (1H, d, *J* = 11.10 Hz, Val-α-**H**), 4.65 (1H, dq, *J* = 8.35, 6.95 Hz, Ala-α-**H**), 4.88 (1H, s, C_{12}-**H**), 4.90 (1H, s, C_{12}-**H**), 5.10 (1H, d, *J* = 10.15 Hz, C_5-**H**), 5.17 (1H, d, *J* = 10.15 Hz, C**H**$_2$=CHCH_2O-), 5.26 (1H, s, C_9-**H**), 5.27 (1H, d, *J* = 12.00 Hz,

C**H**$_2$=CHCH$_2$O-), 5.72 (1H, d, *J* = 8.35 Hz, Ala-N**H**), 5.88 (1H, s, C$_7$-**H**), 5.84-5.92 (1H, m, CH$_2$=C**H**CH$_2$O-), 6.83 (1H, broad t, *J* = 5.05 Hz, Gly-N**H**) ppm;

^{13}C NMR (125 MHz, CDCl$_3$): δ 12.5 (-**C**H$_3$), 16.9 (-**C**H$_3$), 17.7 (-**C**H$_3$), 18.2 (-**C**H$_3$), 18.3 (-**C**H$_3$), 19.5 (-**C**H$_3$), 25.4 (-**C**H-(CH$_3$)$_2$), 30.4 (-N-**C**H$_3$), 30.8 (-C(**C**H$_3$)$_3$), 32.5 (-**C**(CH$_3$)$_3$), 37.0 (-**C**H$_2$-CH$_2$OH), 41.1 (NH-**C**H$_2$-), 42.0 (-**C**H-CH$_3$), 47.2 (-NH-**C**H-CH$_3$), 60.2 (-**C**H$_2$-O-), 62.6 (-N-**C**H-CH(CH$_3$)$_2$), 65.6 (-**C**H$_2$-O-), 83.9 (-**C**H-O-), 111.8 (-C=**C**H$_2$), 117.6 (-CH=**C**H$_2$), 129.7 (-**C**=CH-), 130.3 (-**C**=CH-), 132.7 (-**C**H=CH$_2$), 136.8 (-**C**H=C-), 141.1 (-**C**H=C-), 147.4 (-**C**=CH$_2$-), 155.4 (-**C**=O), 168.3 (-**C**=O), 170.1 (-**C**=O), 174.1 (-**C**=O) ppm;

IR (neat, cm^{-1}): 3320, 3073, 2961, 1727, 1641, 1523, 1464;

HRMS (ESI) m/z (M$^+$+Na): obsd 614.3765, calcd 614. 3781 for $C_{32}H_{53}NaN_3O_7$.

75c

R$_f$ 0.20 (hexane/ethyl acetate, 1:1);

$[\alpha]^{27}_D$ = -68° (*c* = 2.6, CHCl$_3$);

^{1}H NMR (500 MHz, CDCl$_3$): δ 0.81 (3H, d, *J* = 6.50 Hz, Val-C**H**$_3$), 0.90 (3H, d, *J* = 6.95 Hz, C$_{13}$-C**H**$_3$), 0.95 (3H, d, *J* = 6.45 Hz, Val-C**H**$_3$), 1.12 (9H, s, -C(C**H**$_3$)$_3$), 1.29 (3H, d, *J* = 6.95 Hz, Ala-C**H**$_3$), 1.67 (3H, s, C$_{14}$-C**H**$_3$), 1.77 (3H, s, -C$_{15}$-C**H**$_3$), 2.23-2.31 (3H, m, C$_2$-**H**, Val-(CH$_3$)$_2$C**H**), 2.50 (1H, dq, *J* = 10.65, 6.95 Hz, C$_4$-**H**), 3.02 (3H, s, N-C**H**$_3$), 3.71-3.80 (3H, m, Gly-C**H**$_2$, -C**H**$_2$-OH), 4.04 (1H, dd, *J* = 17.55, 6.45 Hz, Gly-C**H**$_2$), 4.53 (2H, d, *J* = 6.90 Hz, CH$_2$=CHC**H**$_2$O-), 4.54 (1H, d, *J* = 10.60 Hz, Val-α-**H**), 4.64 (1H, dq, *J* = 8.30, 6.95 Hz, Ala-α-**H**), 4.89 (1H, s, C$_{12}$-**H**), 4.91 (1H, s, C$_{12}$-**H**), 5.13 (1H, d, *J* = 10.65 Hz, C$_5$-**H**), 5.19 (1H, d, *J* = 10.65 Hz, C**H**$_2$=CHCH$_2$O-), 5.27 (1H, s, C$_9$-**H**), 5.28 (1H, dd, *J* = 17.25, 1.35 Hz, C**H**$_2$=CHCH$_2$O-), 5.68 (1H, d, *J*

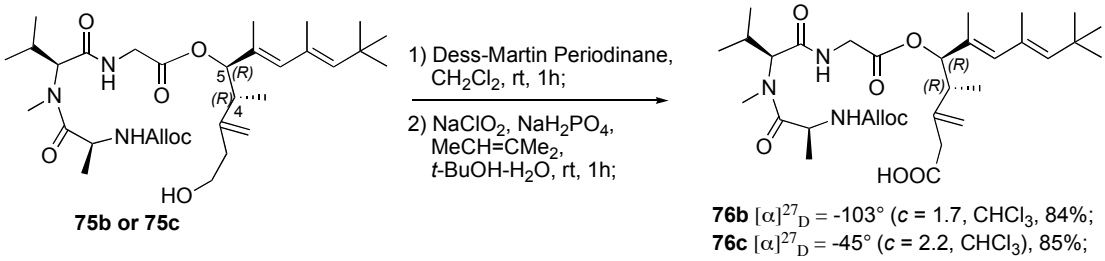
= 8.30 Hz, Ala-N**H**), 5.85-5.90 (1H, m, CH_2=C**H**CH_2O-), 5.92 (1H, s, C_7-**H**), 7.14 (1H, broad t, *J* = 5.05 Hz, Gly-N**H**) ppm;

^{13}C NMR (125 MHz, $CDCl_3$): δ 12.5 (-**C**H_3), 17.3 (-**C**H_3), 17.7 (-**C**H_3), 18.3 (-**C**H_3), 18.4 (-**C**H_3), 19.5 (-**C**H_3), 25.6 (-**C**H-(CH_3)$_2$), 30.5 (-N-**C**H_3), 30.8 (-C(**C**H_3)$_3$), 32.6 (-**C**(CH_3)$_3$), 37.5 (-**C**H_2-CH_2OH), 41.1 (NH-**C**H_2-), 41.4 (-**C**H-CH_3), 47.1 (-NH-**C**H-CH_3), 59.7 (-**C**H_2-O-), 62.7 (-N-**C**H-CH(CH_3)$_2$), 65.6 (-**C**H_2-O-), 84.1 (-**C**H-O-), 111.6 (-C=**C**H_2), 117.6 (-CH=**C**H_2), 129.6 (-**C**=CH-), 130.3 (-**C**=CH-), 132.7 (-**C**H=CH_2), 136.9 (-**C**H=C-), 141.2 (-**C**H=C-), 147.5 (-**C**=CH_2-), 155.4 (-**C**=O), 168.3 (-**C**=O), 169.6 (-**C**=O), 174.1 (-**C**=O) ppm;

IR (neat, cm^{-1}): 3320, 3073, 2961, 1727, 1641, 1523, 1464;

HRMS (ESI) m/z (M^++Na): obsd 614.3765, calcd 614. 3781 for $C_{32}H_{53}NaN_3O_7$.

(7*S*,10*S*,16*R*,17*R*)-10-isopropyl-7,9,17-trimethyl-18-methylene-5,8,11,14-tetraoxo-16-((2*E*,4*E*)-4,6,6-trimethylhepta-2,4-dien-2-yl)-4,15-dioxa-6,9,12-triazaicos-1-en-20-oic acid (76b) and (7*S*,10*S*,16*S*,17*S*)-10-isopropyl-7,9,17-trimethyl-18-methylene-5,8,11,14-tetraoxo-16-((2*E*,4*E*)-4,6,6-trimethylhepta-2,4-dien-2-yl)-4,15-dioxa-6,9,12-triazaicos-1-en-20-oic acid (76c)



75b or 75c

76b $[\alpha]^{27}_D$ = -103° (*c* = 1.7, $CHCl_3$, 84%;
76c $[\alpha]^{27}_D$ = -45° (*c* = 2.2, $CHCl_3$), 85%;

Dess-Martin periodinane oxidation: To a solution of Dess-Martin reagent (48 mg, 0.114 mmol) in anhydrous CH_2Cl_2 (1 mL) was added dropwise of **75b** in CH_2Cl_2 at 0 °C. The reaction mixture was stirred under nitrogen at 0 °C for 2h. After completion, the reaction mixture was diluted with ether and poured slowly into a $Na_2S_2O_3$:$NaHCO_3$ (1:1) solution and stirred for 5 minutes and extract with ether. The

combine etherate layer was washed with $NaHCO_3$, brine and dried over anhydrous $MgSO_4$. Concentration in *vacuo* provided the aldehyde and directly used for next step without purification.

The crude aldehyde was dissolved in a mixture of *t*-BuOH and 2-methyl-2-butene (3:1, 9 mL), and pH=4 NaH_2PO_4 water solution (3 mL) was added, followed by $NaClO_2$ (9.3 mg, 0.084 mmol). The mixture was stirred at room temperature for half an hour, pour into ice-water and extracted with ethyl acetate (3x). The combine organic layer was washed with brine, dried over $MgSO_4$ and concentrated. Purification through flash column chromatography provided **76b** as a colorless oil (38.6 mg, 84%).

76b

$\mathbf{R}_f$ 0.02 (hexane/ethyl acetate, 1:1);

$[\alpha]^{27}_D$ = -103° (*c* = 1.7, $CHCl_3$);

^{1}H NMR (500 MHz, $CDCl_3$): δ 0.83 (3H, d, *J* = 6.95 Hz, Val-C**H**$_3$), 0.93 (3H, d, *J* = 7.4 Hz, C_{13}-C**H**$_3$), 0.94 (3H, d, *J* = 6.45 Hz, Val-C**H**$_3$), 1.12 (9H, s, -C(C**H**$_3$)$_3$), 1.30 (3H, d, *J* = 6.95 Hz, Ala-C**H**$_3$), 1.60 (3H, d, *J* = 1.4 Hz, C_{14}-C**H**$_3$), 1.77 (3H, d, *J* = 1.35 Hz, C_{15}-C**H**$_3$), 2.27 (1H, m, C_4-**H**), 2.65 (1H, m, Val-(CH$_3$)$_2$C**H**), 3.13 (3H, s, N-C**H**$_3$), 3.61 (1H, dd, *J* = 17.35, 3.70 Hz, Gly-C**H**$_2$), 4.32 (1H, dd, *J* = 18.05, 7.85 Hz, Gly-C**H**$_2$), 4.54 (2H, d, *J* = 4.65 Hz, CH_2=CHC**H**$_2$-), 4.71 (1H, d, *J* = 11.55 Hz, Val-α-**H**), 4.71 (1H, m, Ala-α-**H**), 5.03 (1H, s, C_{12}-**H**), 5.07 (1H, s, C_{12}-**H**), 5.10 (1H, d, *J* = 11.1 Hz, C_5-**H**), 5.20 (1H, d, *J* = 10.15 Hz, C**H**$_2$=CHCH$_2$-), 5.27 (1H, d, *J* = 0.95 Hz, C_9-**H**), 5.30 (1H, dd, *J* = 9, 1.4 Hz, C**H**$_2$=CHCH$_2$-), 5.60 (1H, d, *J* = 7.85 Hz, Ala-N**H**), 5.88 (1H, m, CH_2=C**H**CH$_2$-), 5.93 (1H, s, C_7-**H**), 7.19 (1H, brs, *J* = 4.65 Hz, Gly-N**H**) ppm;

^{13}C NMR (125 MHz, $CDCl_3$): δ 12.4 (-**C**H_3), 17.7 (-**C**H_3), 18.1 (-**C**H_3), 18.5 (-**C**H_3), 19.3 (-**C**H_3), 26.1 (-**C**H-$(CH_3)_2$), 26.3 (-**C**H_3), 30.8 (-C(**C**$H_3)_3$), 30.9 (-**C**H_3), 32.6 (-**C**$(CH_3)_3$), 40.2 (-**C**H_2-), 41.3 (-**C**H-), 42.2 (-**C**H_2-), 47.2 (-**C**H-), 62.8 (-**C**H-), 65.7 (-**C**H_2-O-), 84.2 (-**C**H-O-), 114.8 (-C=**C**H_2), 117.8 (-CH=**C**H_2), 129.3 (-**C**=CH-), 130.3 (-**C**=CH-), 132.6 (-**C**H=CH_2), 137.3 (-**C**H=C-), 141.3 (-**C**H=C-), 144.3 (-**C**=CH_2-), 155.5 (-**C**=O), 167.9 (-**C**=O), 169.9 (-**C**=O), 174.5 (-**C**=O), 174.6 (-**C**=O) ppm;

IR (neat, cm^{-1}): 3317, 3086, 2965, 2877, 1722, 1634, 1538, 1455, 1413;

HRMS (ESI) m/z (M^++Na): obsd 628.3562, calcd 628.3574 for $C_{32}H_{51}NaN_3O_8$.

76c

R_f 0.02 (hexane/ethyl acetate, 1:1);

$[\alpha]^{27}_D$ = -45° (*c* = 2.2, $CHCl_3$);

^{1}H NMR (500 MHz, $CDCl_3$): δ 0.83 (3H, d, *J* = 6.9 Hz, Val-C**H**$_3$), 0.92 (3H, d, *J* = 6.9 Hz, C_{13}-C**H**$_3$), 0.97 (3H, d, *J* = 6 Hz, Val-C**H**$_3$), 1.12 (9H, s, -C(C**H**$_3)_3$), 1.33 (3H, d, *J* = 6.45 Hz, Ala-C**H**$_3$), 1.66 (3H, d, *J* = 1.4 Hz, C_{14}-C**H**$_3$), 1.78 (3H, d, *J* = 0.95 Hz, C_{15}-C**H**$_3$), 2.29 (1H, m, C_4-**H**), 2.65 (1H, m, Val-$(CH_3)_2$C**H**), 3.07 (3H, s, N-C**H**$_3$), 3.78 (1H, dd, *J* = 16.88, 4.6 Hz, Gly-C**H**$_2$), 4.11 (1H, dd, *J* = 18.05, 6.45 Hz, Gly-C**H**$_2$), 4.55 (2H, d, *J* = 4.65 Hz, CH_2=CHC**H**$_2$-), 4.66 (1H, d, *J* = 11.1 Hz, Val-α-**H**), 4.69 (1H, m, Ala-α-**H**), 5.04 (1H, s, C_{12}-**H**), 5.07 (1H, s, C_{12}-**H**), 5.12 (1H, d, *J* = 10.65 Hz, C_5-**H**), 5.20 (1H, dd, *J* = 10.63, 1.4 Hz, C**H**$_2$=CHCH_2-), 5.28 (1H, d, *J* = 1.35 Hz, C_9-**H**), 5.28 (1H, m, C**H**$_2$=CHCH_2-), 5.61 (1H, d, *J* = 7.4 Hz, Ala-N**H**), 5.88 (1H, m, CH_2=C**H**CH_2-), 5.93 (1H, s, C_7-**H**), 6.97 (1H, brt, *J* = 5.05 Hz, Gly-N**H**) ppm;

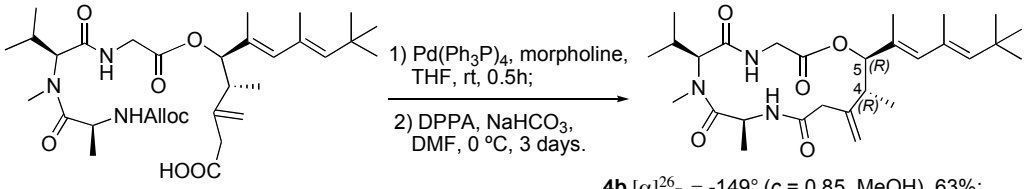
^{13}C NMR (125 MHz, $CDCl_3$): δ 12.4 (-**C**H_3), 17.9 (-**C**H_3), 18.4 (-**C**H_3), 19.5 (-**C**H_3), 19.6 (-**C**H_3), 25.8 (-**C**H-$(CH_3)_2$), 25.9 (-**C**H_3), 30.8 (-C(**C**$H_3)_3$), 30.9 (-**C**H_3), 32.6 (-

C$(CH_3)_3$), 40.8 (-**C**H_2-), 41.4 (-**C**H_2-), 41.4 (-**C**H-), 47.2 (-**C**H-), 63.0 (-**C**H-), 65.7 (-**C**H_2-O-), 83.8 (-**C**H-O-), 115.1 (-C=**C**H_2), 117.7 (-CH=**C**H_2), 129.4 (-**C**=CH-), 130.4 (-**C**=CH-), 132.6 (-**C**H=CH_2), 137.1 (-**C**H=C-), 141.3 (-**C**H=C-), 144.0 (-**C**=CH_2-), 155.5 (-**C**=O), 167.8 (-**C**=O), 169.5 (-**C**=O), 174.1 (-**C**=O), 174.7 (-**C**=O) ppm;

IR (neat, cm^{-1}): 3317, 3086, 2965, 2877, 1722, 1634, 1538, 1455, 1413;

HRMS (ESI) m/z (M^++Na): obsd 628.3562, calcd 628.3574 for $C_{32}H_{51}NaN_3O_8$.

(4*R*,5*R*)-antillatoxin (4b)



76b

4b $[\alpha]^{26}_D$ = -149° (*c* = 0.85, MeOH), 63%;
Literature value : **4b** : $[\alpha]^{21}_D$ = -147° (*c* = 0.23, MeOH);
4a : $[\alpha]^{25}_D$ = -8.7° (*c* = 0.1, MeOH);

To a solution of the acid **76b** (78 mg, 0.128 mmol) in 1 mL THF was added morpholine (0.11 mL, 1.28 mmol) and $Pd(PPh_3)_4$ (15 mg, 0.015 mmol). After stirring for 30 min at room temperature, the mixture was diluted with pH=6 buffer solution and extracted with $CHCl_3$ (x3). The combine organic extract was dried (Na_2SO_4), filtered and concentrated to afford the crude amino acid.

The crude amino acid was dissolved in DMF (50 mL) and cooled to 0 °C. $NaHCO_3$ (50 mg, 0.706 mmol) and DPPA (72 μL, 0.321 mmol) were added, the mixture solution was stirred at 0 °C for 3 days. The solution was diluted with ethyl acetate, wash with $KHSO_4$ solution, H_2O, $NaHCO_3$ and brine. The organic layer was dried (Na_2SO_4), filtered and concentrated. The crude product was purified by flash chromatography on silica gel (Hexane/ethyl acetate, 5:1 to 2:1) to give the desired product as a colorless oil (40.7 mg, 63%).

(4*R*, 5*R*)-antillatoxin (4b)

R_f 0.62 (hexane/ethyl acetate, 1:1);

$[\alpha]^{26}_{D}$ = -149° (*c* = 0.85, MeOH);

^{1}H NMR (500 MHz, $CDCl_3$): δ 0.85 (3H, d, *J* = 6.95 Hz, Val-C**H**$_3$), 0.86 (3H, d, *J* = 7.4 Hz, C_{13}-C**H**$_3$, 0.96 (3H, d, *J* = 6.05 Hz, Val-C**H**$_3$), 1.11 (9H, s, -C(C**H**$_3$)$_3$), 1.40 (3H, d, *J* = 6.5 Hz, Ala-C**H**$_3$), 1.54 (3H, d, *J* = 1.4 Hz, C_{14}-C**H**$_3$), 1.77 (3H, d, *J* = 1.4 Hz, C_{15}-C**H**$_3$), 2.17 (1H, m, C_4-**H**), 2.42 (1H, m, Val-(CH$_3$)$_2$C**H**), 2.83 (1H, d, *J* = 13.4 Hz, C_2-**H**), 2.85 (3H, s, N-C**H**$_3$), 2.97 (1H, d, *J* = 12.95 Hz, C_2-**H**), 3.47 (1H, dd, *J* = 18.28, 1.4 Hz, Gly-C**H**$_2$), 4.25 (1H, d, *J* = 11.05 Hz, Val-α-**H**), 4.67 (1H, dd, *J* = 18.28, 9.92 Hz, Gly-C**H**$_2$), 4.99 (1H, s, C_{12}-**H**), 5.04 (1H, s, C_{12}-**H**), 5.16 (1H, d, *J* = 11.1 Hz, C_5-**H**), 5.28 (1H, s, C_9-**H**), 5.33 (1H, m, Ala-α-**H**), 5.92 (1H, s, C_7-**H**), 6.76 (1H, d, *J* = 9.25 Hz, Ala-N**H**), 7.96 (1H, d, *J* = 9.25 Hz, Gly-N**H**) ppm;

^{13}C NMR (125 MHz, $CDCl_3$): δ 12.4 (-**C**H$_3$), 17.7 (-**C**H$_3$), 18.5 (-**C**H$_3$), 18.6 (-**C**H$_3$), 18.9 (-**C**H$_3$), 19.3 (-**C**H$_3$), 26.1 (-**C**H(CH$_3$)$_2$), 28.7 (-**C**H$_3$), 30.8 (-C(**C**H$_3$)$_3$), 32.6 (-**C**(CH$_3$)$_3$), 38.9 (-**C**H-), 41.1 (-**C**H$_2$-), 43.0 (-**C**H-), 46.5 (-**C**H$_2$-), 67.1 (-**C**H-), 83.4 (-**C**H-O-), 113.7 (-C=**C**H$_2$), 129.1 (-**C**=CH-), 130.4 (-**C**=CH-), 137.2 (-**C**H=C-), 141.4 (-**C**H=C-), 144.8 (-**C**=CH$_2$-), 167.6 (-**C**=O), 167.8 (-**C**=O), 171.0 (-**C**=O), 173.1 (-**C**=O) ppm;

IR (neat, cm^{-1}): 3304, 1744, 1682, 1622, 1547;

HRMS (ESI) m/z [(M+Na)$^+$]: obsd 526.3258, calcd 526.3257 for $C_{28}H_{45}N_3O_5Na$.

(4*S*, 5*S*)-antillatoxin (4c)

$[\alpha]^{25}_{D}$ = -8.7° (*c* = 0.1, MeOH);

^{1}H NMR ($CDCl_3$, 500 MHz): δ 0.85 (3H, d, *J* = 7.0 Hz, Val-C**H**$_3$), 0.90 (3H, d, *J* = 7.0 Hz, C_{13}-C**H**$_3$), 0.95 (3H, m, Val-C**H**$_3$), 0.99 (1H, d, *J* = 6.7 Hz, C_4-**H**), 1.14 (9H, s,

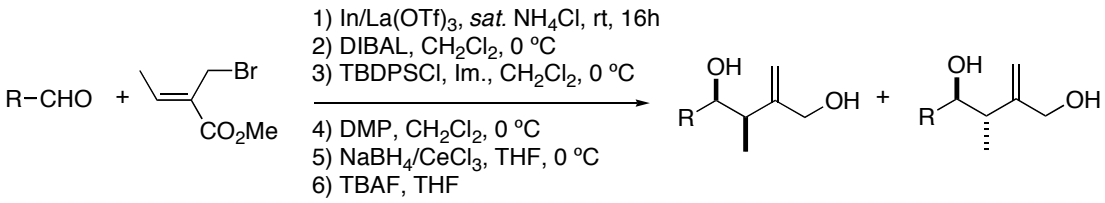
-C(C**H**$_3$)$_3$), 1.38 (3H, d, *J* = 6.7 Hz, Ala-C**H**$_3$), 1.78 (3H, s, C$_{14}$-C**H**$_3$), 1.88 (3H, s, C$_{15}$-C**H**$_3$), 2.40 (1H, m, Val-(CH$_3$)$_2$C**H**), 2.86 (3H, s, N-C**H**$_3$), 3.00 (1H, m, C$_2$-**H**), 3.15 (1H, m, C$_2$-**H**), 3.94 (1H, dd, *J* = 10.4, 7.3 Hz, Gly-C**H**$_2$), 4.03 (1H, dd, *J* = 17.4, 4.6 Hz, Val-α-**H**), 4.52 (1H, d, *J* = 11.3 Hz, Gly-C**H**$_2$), 4.89 (1H, s, C$_{12}$-**H**), 4.93 (1H, s, C$_9$-**H**), 5.21 (2H, m, C$_5$-**H**,C$_{12}$-**H**), 5.32 (1H, m, Ala-α-**H**), 6.01 (1H, s, C$_7$-**H**), 6.52 (1H, d, *J* = 10.1 Hz, Ala-N**H**), 7.54 (1H, br, Gly-N**H**) ppm.

^{13}C NMR (125 MHz, CDCl$_3$): δ 12.9 (-**C**H$_3$), 17.8 (-**C**H$_3$), 18.3 (-**C**H$_3$), 18.5 (-**C**H$_3$), 19.3 (-**C**H$_3$), 26.5 (-**C**H$_3$), 29.1 (-**C**H-(CH$_3$)$_2$), 29.7 (-**C**H$_3$), 30.9 (-C(**C**H$_3$)$_3$), 34.2 (-**C**(CH$_3$)$_3$), 40.6 (-**C**H-), 42.9 (-**C**H$_2$-), 43.2 (-**C**H-), 43.5 (-**C**H$_2$-), 65.9 (-**C**H-), 83.7 (-**C**H-O-), 105.3 (-C=**C**H$_2$), 129.4 (-**C**=CH-), 130.4 (-**C**H=C-), 136.8 (-**C**=CH-), 141.3 (-**C**H=C-), 146.0 (-**C**=CH$_2$-), 166.4 (-**C**=O), 168.2 (-**C**=O), 171.6 (-**C**=O), 172.7 (-**C**=O) ppm.

IR (neat, cm^{-1}): 3304, 1744, 1682, 1622, 1547;

HRMS (ESI) m/z [(M+Na)$^+$]: obsd 526.3258, calcd 526.3257 for C$_{28}$H$_{45}$N$_3$O$_5$Na.

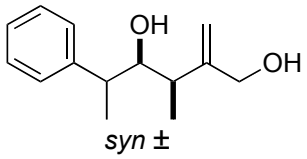
General procedure to synthesis the diol for zebra fish testing:



To a 25 mL rounded bottom flask were added indium (0.11 g, 1 mmol), *sat*. NH$_4$Cl solution (3 mL) and allylic bromide (0.58 g, 3 mmol). After the mixture was stirred at room temperature for 30 minutes, La(OTf)$_3$ (0.58 g, 1 mmol) and aldehyde (1 mmol) were subsequently added. The mixture was stirred vigorously at room temperature for 16h. After the reaction was completed (monitored by TLC), the reaction mixture was extracted with ethyl acetate. The organic extracts were combined and washed with

sat. $NaHCO_3$ solution, brine, dried over anhydrous Na_2SO_4, and concentrated in *vacuo*. The crude product was purified by flash chromatography on silica gel followed by DIBAL reduction to give the *syn*-diol as a colorless oil. The *anti* isomer was obtained in the following way: selective TBDPSCl protection in the presence of imidazole in DMF, DMP oxidation in CH_2Cl_2 followed by Luche's reduction with $CeCl_3/NaBH_4$ in THF and finally TBAF desilylation gave the desired *anti*-diol.

syn-3-methyl-2-methylene-5-phenylhexane-1,4-diol



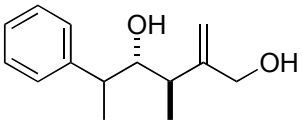
R_f 0.31 (hexane/ethyl acetate, 4:1);

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.02 (3H, d, *J* = 7.32 Hz, -CH-C**H**$_3$), 1.35 (3H, d, *J* = 6.96 Hz, -CH-C**H**$_3$), 2.17 (1H, dq, *J* = 6.96, 2.88 Hz, -C**H**-CH$_3$), 2.84 (1H, dq, *J* = 8.86, 7.32 Hz, -C**H**-CH$_3$), 3.40 (2H, brs, -CH$_2$-O**H**, -CH-O**H**), 3.75 (1H, dd, *J* = 8.86, 2.88 Hz, -C**H**-OH), 3.98 (1H, d, *J* = 13.23 Hz, -C**H**$_2$-OH), 4.07 (1H, d, *J* = 13.23 Hz, -C**H**$_2$-OH), 4.84 (1H, s, -C=C**H**$_2$), 5.07 (1H, d, *J* = 1.05 Hz, -C=C**H**$_2$), 7.14-7.34 (5H, m, -Ph-**H**) ppm;

^{13}C NMR (125 MHz, $CDCl_3$): δ 11.2 (-CH-**C**H$_3$), 18.9 (-CH-**C**H$_3$), 40.1 (-**C**H-CH$_3$), 43.2 (-**C**H-CH$_3$), 64.2 (-**C**H$_2$OH), 78.5 (-**C**HOH), 112.6 (-C=**C**H$_2$), 126.3 (Ph-**C** x2), 127.4 (-Ph-**C** x2), 128.6 (-Ph-**C***p*), 144.9 (-Ph-**C***q*), 151.7 (-**C**=CH$_2$) ppm;

HRMS (ESI) m/z [(M^++Na)]: calcd 243.1361 obsd 243.1371 for $C_{14}H_{20}NaO_2$.

***anti*-3-methyl-2-methylene-5-phenylhexane-1,4-diol**



anti ±

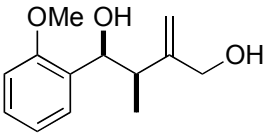
R_f 0.32 (hexane/ethyl acetate, 4:1);

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.14 (3H, d, *J* = 6.96 Hz, -CH-C**H**$_3$), 1.27 (3H, d, *J* = 6.96 Hz, -CH-C**H**$_3$), 2.66 (1H, dq, *J* = 6.96, 2.65 Hz, -C**H**-CH$_3$), 2.86 (1H, dq, *J* = 8.96, 6.96 Hz, -C**H**-CH$_3$), 3.72 (1H, dd, *J* = 8.96, 2.65 Hz, -C**H**-OH), 4.05 (1H, d, *J* = 13.23 Hz, -C**H**$_2$-OH), 4.18 (1H, d, *J* = 13.23 Hz, -C**H**$_2$-OH), 5.03 (1H, s, -C=C**H**$_2$), 5.15 (1H, s, -C=C**H**$_2$), 7.21-7.35 (5H, m, -Ph-**H**) ppm;

^{13}C NMR (125 MHz, $CDCl_3$): δ 11.3 (-CH-**C**H$_3$), 18.5 (-CH-**C**H$_3$), 40.0 (-**C**H-CH$_3$), 43.4 (-**C**H-CH$_3$), 64.6 (-**C**H$_2$OH), 78.2 (-**C**HOH), 113.4 (-C=**C**H$_2$), 126.9 (Ph-**C** x2), 127.9 (-Ph-**C** x2), 128.7 (-Ph-**C***p*), 143.9 (-Ph-**C***q*), 151.9 (-**C**=CH$_2$) ppm;

HRMS (ESI) m/z [(M^++Na)]: calcd 243.1361 obsd 243.1365 for $C_{14}H_{20}NaO_2$.

***syn*-1-(2-methoxyphenyl)-2-methyl-3-methylenebutane-1,4-diol**



syn ±

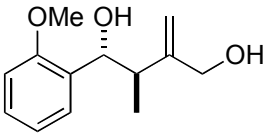
R_f 0.30 (hexane/ethyl acetate, 4:1);

^{1}H NMR (500 MHz, $CDCl_3$): δ 0.96 (3H, d, *J* = 6.96 Hz, CH-C**H**$_3$), 2.68 (1H, dq, *J* = 6.96, 3.84 Hz, -C**H**-CH$_3$), 3.69 (2H, brs, -CH-O**H**, -CH$_2$-O**H**), 3.79 (3H, s, -Ph-OC**H**$_3$), 3.96 (1H, d, *J* = 13.23 Hz, -C**H**$_2$-OH), 4.07 (1H, d, *J* = 13.23 Hz, C**H**$_2$-OH), 4.95 (1H, s, -C=C**H**$_2$), 4.99 (1H, d, *J* = 3.84 Hz, C**H**-OH), 5.06 (1H, s, -C=C**H**$_2$), 6.82 (1H, d, *J* = 8.37 Hz, -Ph-**H***o*), 6.92 (1H, t, *J* = 7.48 Hz, -Ph-**H***p*), 7.20 (1H, td, *J* = 7.83, 1.74 Hz, -Ph-**H***m*), 7.36 (1H, dd, *J* = 7.48, 1.56 Hz, -Ph-**H***m*) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 12.0 (-CH-**C**H_3), 42.6 (-**C**H-CH_3), 55.1 (-Ar-O**C**H_3), 64.5 (-**C**H_2OH), 71.8 (-**C**HOH), 110.0 (-Ph-**C**), 112.3 (-C=**C**H_2), 120.2 (-Ph-**C**), 127.3 (-Ph-**C**), 127.7 (-Ph-**C**), 130.9 (-C=**C**H_2), 151.2 (-**C**=CH_2), 155.7 (-**C**-OMe);

HRMS (ESI) m/z [M^+]: calcd 222.1256 obsd 222.1251 for $C_{13}H_{18}O_3$.

***anti*-1-(2-methoxyphenyl)-2-methyl-3-methylenebutane-1,4-diol**



anti ±

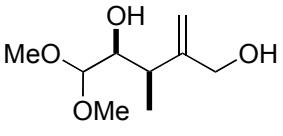
R_f 0.24 (hexane/ethyl acetate, 4:1);

^{1}H NMR (500 MHz, $CDCl_3$): δ 0.94 (3H, d, *J* = 7.32 Hz, -CH-C**H**$_3$), 2.76 (1H, dq, *J* = 7.32, 8.73 Hz, -C**H**-CH_3), 2.99 (2H, brs, -CH-O**H**, -CH_2-O**H**), 3.85 (3H, s, -Ph-OC**H**$_3$), 4.06 (1H, d, *J* = 12.54 Hz, -C**H**$_2$-OH), 4.18 (1H, d, *J* = 12.54 Hz, -C**H**$_2$-OH), 4.83 (1H, d, *J* = 8.73 Hz, -C**H**-OH), 5.01 (1H, s, -C=C**H**$_2$), 5.19 (1H, d, *J* = 1.41 Hz, -C=C**H**$_2$), 6.88 (1H, d, *J* = 8.01 Hz, -Ph-**H***o*), 6.95 (1H, td, *J* = 7.48, 1.05 Hz, -Ph-**H***p*), 7.25 (1H, td, *J* = 8.10, 1.74 Hz, -Ph-**H***m*), 7.30 (1H, dd, *J* = 7.68, 1.74 Hz, -Ph-**H***m*) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 17.4 (-CH-**C**H_3), 44.7 (-**C**H-CH_3), 55.3 (-Ph-O**Me**), 65.3 (-**C**H_2OH), 74.3 (-**C**HOH), 110.5 (-Ph-**C**), 113.3 (-C=**C**H_2), 120.7 (-Ph-**C**), 127.9 (-Ph-**C**), 128.5 (-Ph-**C**), 130.8 (-C=**C**H_2), 151.2 (-**C**=CH_2), 156.7 (-**C**-OMe) ppm;

HRMS (ESI) m/z [M^+]: calcd 222.1256 obsd 222.1252 for $C_{13}H_{18}O_3$.

***syn*-5,5-dimethoxy-3-methyl-2-methylenepentane-1,4-diol**



syn ±

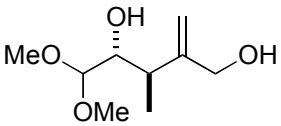
R_f 0.26 (hexane/ethyl acetate, 4:1);

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.13 (3H, d, *J* = 7.32 Hz, -CH-C**H**$_3$), 2.34 (1H, brs, -CH-O**H**), 2.67 (1H, dq, *J* = 7.30, 4.44 Hz, -C**H**-CH$_3$), 3.38 (3H, s, -C-OC**H**$_3$), 3.41 (3H, s, -C-OC**H**$_3$), 3.50 (1H, dd, *J* = 6.60, 4.44 Hz, -C**H**-OH), 3.86 (1H, brs, -CH-O**H**), 3.93 (1H, d, *J* = 12.54 Hz, -C**H**$_2$-OH), 4.11 (1H, d, *J* = 12.54 Hz, -C**H**$_2$-OH), 4.21 (1H, d, *J* = 6.60 Hz, -C**H**-OMe), 4.96 (1H, d, *J* = 2.1 Hz, -C=C**H**$_2$), 5.10 (1H, brs, -C=C**H**$_2$) ppm;

^{13}C NMR (125 MHz, $CDCl_3$): δ 16.6 (-CH-**C**H$_3$), 40.2 (-**C**H-CH$_3$), 54.5 (-O**Me**), 54.9 (-O**Me**), 63.8 (-**C**H$_2$OH), 73.8 (-**C**HOH), 105.0 (-**C**H-OMe), 115.6 (-C=**C**H$_2$), 149.1 (-**C**=CH$_2$) ppm;

HRMS (FAB) m/z [(M^+-1)]: calcd 189.1127 obsd 189.1129 for $C_9H_{17}O_4$.

***anti*-5,5-dimethoxy-3-methyl-2-methylenepentane-1,4-diol**



anti ±

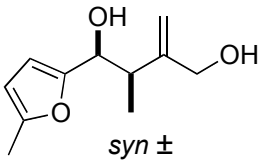
R_f 0.13 (hexane/ethyl acetate, 4:1);

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.08 (3H, d, *J* = 6.96 Hz, -CH-C**H**$_3$), 2.37 (1H, brs, -CH-O**H**), 2.54 (1H, dq, *J* = 6.96, 3.81 Hz, -C**H**-CH$_3$), 3.06 (1H, brs, -CH-O**H**), 3.37 (3H, s, -C-OC**H**$_3$), 3.40 (3H, s, -C-OC**H**$_3$), 3.64 (1H, dd, *J* = 6.27, 3.81 Hz, -C**H**-OH), 4.00 (1H, d, *J* = 13.26 Hz, -C**H**$_2$-OH), 4.11 (1H, d, *J* = 13.26 Hz, -C**H**$_2$-OH), 4.24 (1H, d, *J* = 6.27 Hz, -C**H**-OMe), 4.95 (1H, brs, -C=C**H**$_2$), 5.08 (1H, d, *J* = 1.38 Hz, -C=C**H**$_2$) ppm;

^{13}C NMR (125 MHz, $CDCl_3$): δ 13.1 (-CH-**C**H_3), 39.1 (-**C**H-CH_3), 54.4 (-O**Me**), 54.5 (-O**Me**), 64.6 (-**C**H_2OH), 73.1 (-**C**HOH), 104.5 (-**C**H-OMe), 112.8 (-C=**C**H_2), 151.0 (-**C**=CH_2) ppm;

HRMS (ESI) m/z [(M^++Na)]: calcd 213.1103 obsd 213.1104 for $C_9H_{18}NaO_4$.

***syn*-2-methyl-3-methylene-1-(5-methylfuran-2-yl)butane-1,4-diol**



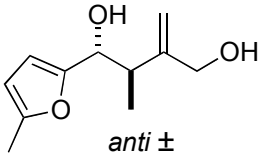
R_f 0.27 (hexane/ethyl acetate, 4:1);

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.08 (3H, d, *J* = 7.32 Hz, -CH-C**H**$_3$), 2.23 (3H, s, -C-C**H**$_3$), 2.73 (1H, dq, *J* = 7.32, 4.53 Hz, -C**H**-CH_3), 3.68 (1H, brs, -CH_2-O**H**), 3.93 (1H, d, *J* = 13.23 Hz, -C**H**$_2$-OH), 4.05 (1H, d, *J* = 13.23 Hz, -C**H**$_2$-OH), 4.65 (1H, d, *J* = 4.53 Hz, -C**H**-OH), 4.94 (1H, s, -C=C**H**$_2$), 5.07 (1H, s, -C=C**H**$_2$), 5.85 (1H, brs, -C**H**=C), 6.06 (1H, d, *J* = 3.15 Hz, -C**H**=C) ppm;

^{13}C NMR (125 MHz, $CDCl_3$): δ 13.4 (-CH-**C**H_3), 13.8 (-CH-**C**H_3), 42.8 (-**C**H-CH_3), 64.8 (-**C**H_2OH), 71.4 (-**C**HOH), 105.9 (-**C**H=C-), 107.0 (-**C**H=C-), 113.3 (-C=**C**H_2), 150.2 (-**C**=CH_2), 151.0 (-CH=**C**-), 153.6 (-CH=**C**-) ppm;

HRMS (ESI) m/z [M^+]: calcd 196.1099 obsd 196.1093 for $C_{11}H_{16}O_3$.

***anti* - 2-methyl-3-methylene-1-(5-methylfuran-2-yl)butane-1,4-diol**



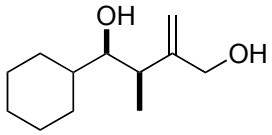
R_f 0.21 (hexane/ethyl acetate, 4:1);

^{1}H NMR (500 MHz, $CDCl_3$): δ 0.95 (3H, d, *J* = 6.99 Hz, -CH-C**H**$_3$), 2.27 (3H, s, -C-C**H**$_3$), 2.81 (1H, dq, *J* = 8.71, 6.99 Hz, -C**H**-CH$_3$), 3.12 (1H, brs, -CH$_2$-O**H**), 4.06 (1H, d, *J* = 12.87 Hz, -C**H**$_2$-OH), 4.15 (1H, d, *J* = 12.87 Hz, -C**H**$_2$-OH), 4.48 (1H, d, *J* = 8.71 Hz, -C**H**-OH), 5.07 (1H, s, -C=C**H**$_2$), 5.19 (1H, s, -C=C**H**$_2$), 5.88 (1H, d, *J* = 2.4 Hz, -C**H**=C), 6.13 (1H, d, *J* = 3.12 Hz, -C**H**=C) ppm;

^{13}C NMR (125 MHz, $CDCl_3$): δ 13.5 (-CH-**C**H$_3$), 17.2 (-CH-**C**H$_3$), 43.3 (-**C**H-CH$_3$), 65.0 (-**C**H$_2$OH), 71.7 (-**C**HOH), 105.9 (-**C**H=C-), 108.2 (-**C**H=C-), 113.8 (-C=**C**H$_2$), 150.3 (-**C**=CH$_2$), 151.7 (-CH=**C**-), 153.3 (-CH=**C**-) ppm;

HRMS (ESI) m/z [M^+] calcd 196.1099 obsd 196.1099 for $C_{11}H_{16}O_3$.

***syn*-1-cyclohexyl-2-methyl-3-methylenebutane-1,4-diol**



syn ±

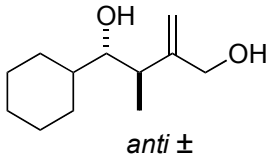
R$_f$ 0.15 (hexane/ethyl acetate, 4:1);

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.07 (3H, d, *J* = 7.4 Hz, CH-C**H**$_3$), 1.18-1.23 (4H, m, c-C_6H_{11}), 1.42-1.48 (1H, m, c-C_6H_{11}), 1.61-1.68 (2H, m, c-C_6H_{11}), 1.74-1.80 (4H, m, c-C_6H_{11}), 2.53 (1H, dq, *J* = 7.40, 6.90 Hz, -C**H**-CH$_3$), 2.60 (2H, brs, -CH-O**H**, CH$_2$-O**H**), 3.26 (1H, dd, *J* = 7.40, 6.90 Hz, C**H**-OH), 4.02 (1H, d, *J* = 12.95 Hz, C**H**$_2$-OH), 4.13 (1H, d, *J* = 12.95 Hz, -C**H**$_2$-OH), 4.99 (1H, s, -C=C**H**$_2$), 5.14 (1H, d, *J* = 0.95 Hz, -C=C**H**$_2$) ppm;

^{13}C NMR (125 MHz, $CDCl_3$): δ 17.4 (-CH-**C**H$_3$), 26.0 (-**C**H$_2$-), 26.1 (-**C**H$_2$-), 26.4 (-**C**H$_2$-), 26.5 (-**C**H$_2$-), 30.5 (-**C**H$_2$-), 40.2 (-**C**H-CH$_3$), 41.0 (-**C**H-CH-OH), 64.7 (-**C**H$_2$OH), 79.2 (-**C**HOH), 113.8 (-C=**C**H$_2$), 151.2 (-**C**=CH$_2$) ppm;

HRMS (ESI) m/z [(M^++Na)]: calcd 221.1517 obsd 221.1516 for $C_{12}H_{22}O_2Na$.

***anti*-1-cyclohexyl-2-methyl-3-methylenebutane-1,4-diol**



anti ±

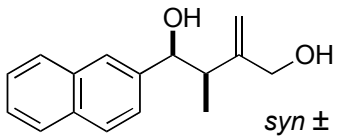
R_f 0.15 (hexane/ethyl acetate, 4:1);

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.03 (3H, d, *J* = 7.4 Hz, -CH-C**H**$_3$), 1.15-1.27 (4H, m, *c*-C_6H_{11}), 1.38-1.43 (1H, m, *c*-C_6H_{11}), 1.64-1.67 (2H, m, *c*-C_6H_{11}), 1.73-1.76 (2H, m, *c*-C_6H_{11}), 1.99-2.02 (2H, m, *c*-C_6H_{11}), 2.14 (2H, brs, -CH-O**H**, -CH_2-O**H**), 2.52 (1H, dq, *J* = 7.4, 3.25 Hz, -C**H**-CH_3), 3.27 (1H, dd, *J* = 8.32, 3.25 Hz, -C**H**-OH), 4.07 (1H, d, *J* = 12.95 Hz, -C**H**$_2$-OH), 4.13 (1H, d, *J* = 12.95 Hz, -C**H**$_2$-OH), 4.98 (1H, s, -C=C**H**$_2$), 5.16 (1H, s, -C=C**H**$_2$) ppm;

^{13}C NMR (125 MHz, $CDCl_3$): δ 11.6 (-CH-**C**H_3), 25.9 (-**C**H_2-), 26.1 (-**C**H_2-), 26.4 (-**C**H_2-), 29.4 (-**C**H_2-), 29.4 (-**C**H_2-), 39.2 (-**C**H-CH_3), 40.3 (-**C**H-CH-OH), 64.8 (-**C**H_2OH), 77.6 (-**C**HOH), 112.5 (-C=**C**H_2), 151.1 (-**C**=CH_2) ppm;

HRMS (ESI) m/z [(M^++Na)]: calcd 221.1517 obsd 221.1516 for $C_{12}H_{22}O_2Na$.

***syn*-2-methyl-3-methylene-1-(naphthalen-2-yl)butane-1,4-diol**



syn ±

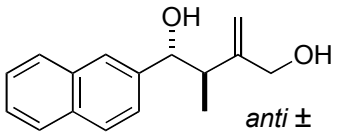
R_f 0.12 (hexane/ethyl acetate, 4:1);

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.01 (3H, d, *J* = 6.9 Hz, -CH-C**H**$_3$), 2.71 (1H, dq, *J* = 6.9, 3.7 Hz, -C**H**-CH_3), 3.96 (1H, d, *J* = 12.95 Hz, -C**H**$_2$-OH), 4.07 (1H, d, *J* = 12.95 Hz, -C**H**$_2$-OH), 4.25 (2H, brs, -CH-O**H**, -CH_2-O**H**), 4.90 (1H, d, *J* = 3.7 Hz, -C**H**-OH), 4.94 (1H, s, -C=C**H**$_2$), 5.11 (1H, d, *J* = 0.95 Hz, -C=C**H**$_2$), 7.41 (1H, dd, *J* = 1.4, 8.32 Hz, -Ph-**H**), 7.47 (2H, m, -Ph-**H**), 7.79 (4H, m, -Ph-**H**) ppm;

^{13}C NMR (125 MHz, $CDCl_3$): δ 12.6 (-CH-**C**H_3), 45.0 (-**C**H-CH_3), 64.8 (-**C**H_2OH), 76.4 (-**C**HOH), 113.7 (-C=**C**H_2), 124.5 (-Ph-**C**), 124.8 (-Ph-**C**), 125.5 (-Ph-**C**), 125.8 (-Ph-**C**), 127.4 (-Ph-**C**), 127.5 (-Ph-**C**), 127.8 (-Ph-**C**), 132.6 (-Ph-**C***q*), 132.9 (-Ph-**C***q*), 140.1 (-Ph-**C***q*), 150.3 (-**C**=CH_2) ppm;

HRMS (ESI) m/z [M^+]: calcd 242.1307 obsd 242.1258 found $C_{16}H_{18}O_2$.

***anti*-2-methyl-3-methylene-1-(naphthalen-2-yl)butane-1,4-diol**



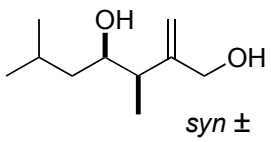
R_f 0.08 (hexane/ethyl acetate, 4:1);

^{1}H NMR (500 MHz, $CDCl_3$): δ 0.93 (3H, d, *J* = 6.95 Hz, -CH-C**H**$_3$), 2.73 (1H, dq, *J* = 8.80, 6.95 Hz, -C**H**-CH_3), 4.14 (1H, d, *J* = 12.93 Hz, -C**H**$_2$-OH), 4.22 (1H, d, *J* = 12.93 Hz, -C**H**$_2$-OH), 4.68 (1H, d, *J* = 8.8 Hz, -C**H**-OH), 5.10 (1H, s, -C=C**H**$_2$), 5.24 (1H, d, *J* = 0.95 Hz, -C=C**H**$_2$), 7.47 (3H, m, -Ph-**H**), 7.82 (4H, m, -Ph-**H**) ppm;

^{13}C NMR (125 MHz, $CDCl_3$): δ 17.5 (-CH-**C**H_3), 45.7 (-**C**H-CH_3), 65.4 (-**C**H_2OH), 78.9 (-**C**HOH), 113.7 (-C=**C**H_2), 124.5 (-Ph-**C**), 125.4 (-Ph-**C***q*), 125.9 (-Ph-**C**), 126.0 (-Ph-**C**), 126.1 (-Ph-**C**), 127.7 (-Ph-**C**), 127.9 (-Ph-**C**), 128.2 (-Ph-**C**), 133.2 (-Ph-**C***q*), 140.3 (-Ph-**C***q*), 150.8 (-**C**=CH_2) ppm;

HRMS (ESI) m/z [(M^++Na)]: calcd 265.1204 obsd 265.1204 for $C_{16}H_{18}NaO_2$.

***syn*-3,6-dimethyl-2-methyleneheptane-1,4-diol**



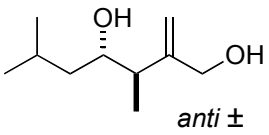
R_f 0.14 (hexane/ethyl acetate, 4:1);

^{1}H NMR (500 MHz, $CDCl_3$): δ 0.88 (3H, d, *J* = 6.45 Hz, -CH-(C**H**$_3$)$_2$), 0.91 (3H, d, *J* = 6.45 Hz, -CH-(C**H**$_3$)$_2$), 1.07 (3H, d, *J* = 7.4 Hz, -CH-C**H**$_3$), 1.24-1.28 (1H, m, -CH-C**H**$_2$-), 1.76-1.84 (1H, m, -CH-C**H**$_2$-), 2.27 (1H, dq, *J* = 7.4, 6.95 Hz, -C**H**-CH$_3$), 2.39 (1H, t, *J* = 7.85 Hz, -C**H**-(CH$_3$)$_2$), 3.02 (2H, brs, -CH-O**H**, -CH$_2$-O**H**), 3.56 (1H, td, *J* = 6.95, 3.25 Hz, -C**H**-OH), 3.99 (1H, d, *J* = 12.95 Hz, -C**H**$_2$-OH), 4.11 (1H, dd, *J* = 12.95, 0.9 Hz, -C**H**$_2$-OH), 4.95 (1H, d, *J* = 1.4 Hz, -C=C**H**$_2$), 5.13 (1H, d, *J* = 0.9 Hz, -C=C**H**$_2$) ppm;

^{13}C NMR (125 MHz, $CDCl_3$): δ 16.9 (-**C**H$_3$), 21.7 (-**C**H$_3$), 23.8 (-**C**H$_3$), 24.5 (-**C**H(CH$_3$)$_2$), 44.3 (-**C**H$_2$CHOH), 45.3 (-**C**H-CH$_3$), 64.3 (-**C**H$_2$OH), 72.7 (-**C**HOH), 114.0 (-C=**C**H$_2$), 150.4 (-**C**=CH$_2$) ppm;

HRMS (ESI) m/z [M$^+$]: calcd 172.1463 obsd 172.1417 for $C_{10}H_{20}O_2$.

***anti*-3,6-dimethyl-2-methyleneheptane-1,4-diol**



anti ±

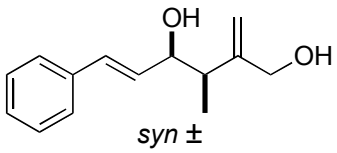
R$_f$ 0.14 (hexane/ethyl acetate, 4:1);

^{1}H NMR (500 MHz, $CDCl_3$): δ 0.90 (3H, d, *J* = 6.95 Hz, -CH-(C**H**$_3$)$_2$), 0.92 (3H, d, *J* = 6.95 Hz, -CH-(C**H**$_3$)$_2$), 1.05 (3H, d, *J* = 7.40 Hz, -CH-C**H**$_3$), 1.36-1.43 (1H, m, -CH-C**H**$_2$-), 1.70-1.78 (1H, m, -CH-C**H**$_2$-), 2.33 (1H, dq, *J* = 7.40, 3.25 Hz, -C**H**-CH$_3$), 2.40 (1H, t, *J* = 7.85 Hz, -C**H**-(CH$_3$)$_2$), 2.75 (2H, brs, -CH-O**H**, -CH$_2$-O**H**), 3.70 (1H, td, *J* = 6.9, 3.25 Hz, -C**H**-OH), 4.03 (1H, dd, *J* = 12.95, 0.95 Hz, -C**H**$_2$-OH), 4.11 (1H, d, *J* = 12.95 Hz, -C**H**$_2$-OH), 4.93 (1H, s, -C=C**H**$_2$), 5.12 (1H, d, *J* = 1.4 Hz, -C=C**H**$_2$) ppm;

^{13}C NMR (125 MHz, $CDCl_3$): δ 12.9 (-**C**H_3), 22.0 (-**C**H_3), 23.5 (-**C**H_3), 24.8 (-**C**$H(CH_3)_2$), 43.3 (-**C**H_2CHOH), 43.3 (-**C**H-CH_3), 65.3 (-**C**H_2OH), 71.9 (-**C**HOH), 112.7 (-C=**C**H_2), 151.4 (-**C**=CH_2) ppm;

HRMS (ESI) m/z [M^+]: calcd 172.1463 obsd 172.1418 for $C_{10}H_{20}O_2$.

***syn*-(*E*)-3-methyl-2-methylene-6-phenylhex-5-ene-1,4-diol**

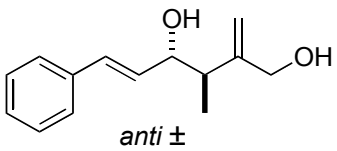


R_f 0.11 (hexane/ethyl acetate, 4:1);

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.11 (3H, d, *J* = 7.32 Hz, -CH-C**H**$_3$), 2.60 (1H, dq, *J* = 3.46, 7.32 Hz, -C**H**-CH_3), 3.13 (2H, brs, -CH-O**H**, -CH_2-O**H**), 4.09 (1H, d, *J* = 12.72 Hz, -C**H**$_2$-OH), 4.17 (1H, d, *J* = 12.72 Hz, -C**H**$_2$-OH), 4.33 (1H, dd, *J* = 6.63, 3.46 Hz, -C**H**-OH), 4.99 (1H, s, -C=C**H**$_2$), 5.19 (1H, s, -C=C**H**$_2$), 6.22 (1H, dd, *J* = 15.66, 6.63 Hz, -C**H**=CH-), 6.58 (1H, d, *J* = 15.66 Hz, -CH=C**H**-), 7.21-7.41 (5H, m, -Ph-**H**) ppm;

^{13}C NMR (125 MHz, $CDCl_3$): δ 14.8 (-CH-**C**H_3), 44.1 (-**C**H-CH_3), 66.7 (-**C**H_2OH), 76.1 (-**C**HOH), 114.6 (-C=**C**H_2), 127.2 (-Ph-**C** x2), 128.3 (-Ph-**C**), 129.3 (-Ph-**C** x2), 130.6 (-**C**H=CH-), 131.8 (-**C**H=CH-), 137.4 (-Ph-**C***q*), 150.8 (-**C**=CH_2) ppm;

***anti*-(*E*)-3-methyl-2-methylene-6-phenylhex-5-ene-1,4-diol**

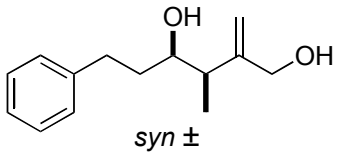


R_f 0.11 (hexane/ethyl acetate, 4:1);

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.12 (3H, d, *J* = 7.32 Hz, -CH-C**H**$_3$), 2.48 (1H, dq, *J* = 7.29, 7.32 Hz, -C**H**-CH_3), 2.59 (2H, brs, -CH-O**H**, -CH_2-O**H**), 4.12 (1H, d, *J* = 12.45 Hz, -C**H**$_2$-OH), 4.20 (1H, d, *J* = 12.45 Hz, -C**H**$_2$-OH), 4.21 (1H, dd, *J* = 7.29, 6.96 Hz, -C**H**-OH), 5.07 (1H, s, -C=C**H**$_2$), 5.22 (1H, d, *J* = 1.05 Hz, -C=C**H**$_2$), 6.21 (1H, dd, *J* = 16.02, 6.96 Hz, -C**H**=CH-), 6.61 (1H, d, *J* = 16.02 Hz, -CH=C**H**-), 7.28-7.40 (5H, m, -Ph-**H**) ppm;

^{13}C NMR (125 MHz, $CDCl_3$): δ 17.7 (-CH-**C**H_3), 45.3 (-**C**H-CH_3), 65.8 (-**C**H_2OH), 77.4 (-**C**HOH), 114.7 (-C=**C**H_2), 127.2 (-Ph-**C** x2), 128.4 (-Ph-**C**), 129.3 (-Ph-**C** x2), 131.5 (-**C**H=CH-), 132.5 (-**C**H=CH-), 137.3 (-Ph-**C***q*), 150.9 (-**C**=CH_2) ppm;

***syn*-3-methyl-2-methylene-6-phenylhexane-1,4-diol**



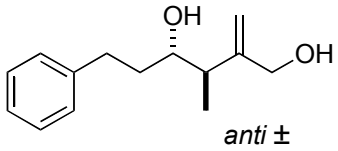
syn ±

R$_f$ 0.16 (hexane/ethyl acetate, 4:1);

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.08 (3H, d, *J* = 7.23 Hz, -CH-C**H**$_3$), 1.72-1.83 (2H, m, -C**H**$_2$-CH_2-), 2.39 (1H, dq, *J* = 7.23, 3.6 Hz, -C**H**-CH_3), 2.51 (2H, brs, -CH-O**H**, -CH_2-O**H**), 2.60-2.70 (1H, m, -C**H**$_2$-CH_2-), 2.79-2.89 (1H, m, -CH_2-C**H**$_2$-), 3.62-3.68 (1H, m, -C**H**-OH), 4.04 (1H, d, *J* = 12.64 Hz, -C**H**$_2$-OH), 4.12 (1H, d, *J* = 12.64 Hz, -C**H**$_2$-OH), 4.95 (1H, s, -C=C**H**$_2$), 5.14 (1H, d, *J* = 1.2 Hz, -C=C**H**$_2$), 7.19-7.31 (5H, m, -Ph-**H**) ppm;

^{13}C NMR (125 MHz, $CDCl_3$): δ 13.7 (-CH-**C**H_3), 33.5 (-**C**H_2-), 36.8 (-**C**H_2-), 43.8 (-**C**H-CH_3), 66.2 (-**C**H_2OH), 73.9 (-**C**HOH), 113.6 (-C=**C**H_2), 126.6 (-Ph-**C**), 129.1 (-Ph-**C** x4), 142.7 (-Ph-**C***q*), 151.9 (-**C**=CH_2) ppm;

***anti*-3-methyl-2-methylene-6-phenylhexane-1,4-diol**



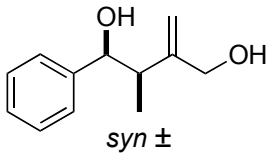
anti ±

R_f 0.16 (hexane/ethyl acetate, 4:1);

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.09 (3H, d, *J* = 6.96 Hz, -CH-C**H**$_3$), 1.64-1.79 (1H, m, -C**H**$_2$-CH$_2$-), 1.82-1.94 (1H, m, -C**H**$_2$-CH$_2$-), 2.37 (1H, quintet, *J* = 6.96 Hz, -C**H**-CH$_3$), 2.49 (2H, brs, -CH-O**H**, -CH$_2$-O**H**), 2.62-2.74 (1H, m, -C**H**$_2$-CH$_2$-), 2.83-2.94 (1H, m, -CH$_2$-C**H**$_2$-), 3.51-3.60 (1H, m, -C**H**-OH), 4.04 (1H, d, *J* = 12.71 Hz, -C**H**$_2$-OH), 4.15 (1H, dd, *J* = 12.71, 1.02 Hz, -C**H**$_2$-OH), 5.01 (1H, s, -C=C**H**$_2$), 5.17 (1H, d, *J* = 1.02 Hz, -C=C**H**$_2$), 7.18-7.29 (5H, m, -Ph-**H**) ppm;

^{13}C NMR (125 MHz, $CDCl_3$): δ 17.5 (-CH-**C**H$_3$), 32.9 (-**C**H$_2$-), 37.5 (-**C**H$_2$-), 45.6 (-**C**H-CH$_3$), 65.3 (-**C**H$_2$OH), 74.8 (-**C**HOH), 114.9 (-C=**C**H$_2$), 126.5 (-Ph-**C**), 129.1 (-Ph-**C** x2), 129.1 (-Ph-**C** x2), 142.9 (-Ph-**C***q*), 151.0 (-**C**=CH$_2$) ppm;

***syn*-2-methyl-3-methylene-1-phenylbutane-1,4-diol**



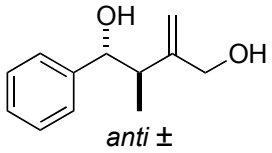
syn ±

R_f 0.14 (hexane/ethyl acetate, 4:1);

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.03 (3H, d, *J* = 7.32 Hz, -CH-C**H**$_3$), 2.38 (2H, brs, -CH-O**H**, -CH$_2$-O**H**), 2.64 (1H, dq, *J* = 4.53, 7.32 Hz, -C**H**-CH$_3$), 4.00 (1H, d, *J* = 13.41 Hz, -C**H**$_2$-OH), 4.11 (1H, d, *J* = 13.41 Hz, -C**H**$_2$-OH), 4.81 (1H, d, *J* = 4.53 Hz, -C**H**-OH), 4.98 (1H, s, -C=C**H**$_2$), 5.17 (1H, d, *J* = 1.02 Hz, -C=C**H**$_2$), 7.26-7.34 (5H, m, -Ph-**H**) ppm;

^{13}C NMR (125 MHz, $CDCl_3$): δ 12.8 (-CH-**C**H_3), 45.1 (-**C**H-CH_3), 65.2 (-**C**H_2OH), 76.6 (-**C**HOH), 113.6 (-C=**C**H_2), 126.2 (-Ph-**C** x2), 127.1 (-Ph-**C**), 127.9 (-Ph-**C** x2), 142.6 (-Ph-**C***q*), 150.6 (-**C**=CH_2) ppm;

***anti*-2-methyl-3-methylene-1-phenylbutane-1,4-diol**



R_f 0.14 (hexane/ethyl acetate, 4:1);

^{1}H NMR (500 MHz, $CDCl_3$): δ 0.89 (3H, d, *J* = 6.95 Hz, -CH-C**H**$_3$), 2.60 (1H, dq, *J* = 8.80, 6.95 Hz, -C**H**-CH_3), 2.81 (2H, brs, -CH-O**H**, -CH_2-O**H**), 4.09 (1H, d, *J* = 12.95 Hz, -C**H**$_2$-OH), 4.17 (1H, d, *J* = 12.95 Hz, -C**H**$_2$-OH), 4.50 (1H, d, *J* = 8.80 Hz, -C**H**-OH), 5.05 (1H, s, -C=C**H**$_2$), 5.21 (1H, s, -C=C**H**$_2$), 7.26-7.34 (5H, m, -Ph-**H**) ppm;

^{13}C NMR (125 MHz, $CDCl_3$): δ 17.3 (-CH-**C**H_3), 45.8 (-**C**H-CH_3), 65.0 (-**C**H_2OH), 78.5 (-**C**HOH), 113.6 (-C=**C**H_2), 126.7 (-Ph-**C** x2), 127.6 (-Ph-**C**), 128.2 (-Ph-**C** x2), 142.9 (-Ph-**C***q*), 150.4 (-**C**=CH_2) ppm;

PART II

Chapter 2

Synthetic Studies Towards The Total Synthesis of Cytochalasans

2.1 Introduction

Cytochalasans are a group of fungal secondary metabolites produced by several different and unrelated fungal species. They are related by structure and biological activity. For example, Cytochalasins A (**1**) and B (**2**) are metabolites of *Helminthosporium dematioideum*;[1] Cytochalasins C (**3**) and D (**4**) are isomeric metabolites of *Metarrhizium anisopliae*;[2] Cytochalasin E (**5**) is a metabolite of *Rosellinia necatrix*; Cytochalasin F (**6**) is a minor metabolite of *Helminthosporium dematioideum*;[3] Cytochalasins H (**7**) and J (**8**) are metabolites of *Phomopsis paspali* found on *Paspalum scrobiculatum*.[4]

The cytochalasans were discovered in 1964 by the Pharmaceuticals Division of Imperial Chemicals Industries, Ltd. The name cytochalasin comes from the Greek words (cytos = cell; chalasis = relaxation) and is coined to describe the unique effects which the compounds produce on mammalian cells in tissue culture.[5]

[1] Aldridge, D. C.; Armstrong, J. J.; Speaks, R. N.; Turner, W. B. *J. Chem. Soc.* **1967**, 1667.
[2] Aldridge, D. C.; Turner, W. B. *J. Chem. Soc.* **1969**, 923.
[3] (a) Aldridge, D. C.; Burrows, F. F.; Turner, W. B. *Chem. Commun.* **1972**, 148. (b) Aldridge, D. C.; Greatbanks, D.; Turner, W. B. *Chem. Commun.* **1973**, 551.
[4] (a) Pendse, G. S. *Experientia* **1974**, *30*, 107. (b) Padwardhan, S. A.; Pandey, R. C.; Dev, S.; Pendse, G. S. *Phytochemistry* **1974**, *13*, 1985. (c) Deshmukh, P. G.; Kanitkar, U. K.; Pendse, G. S. *Acta Microbiol. Acad. Sci. Hung.* **1975**, *22*, 253.
[5] Carter, S. B. *Nature*, **1967**, *213*, 261.

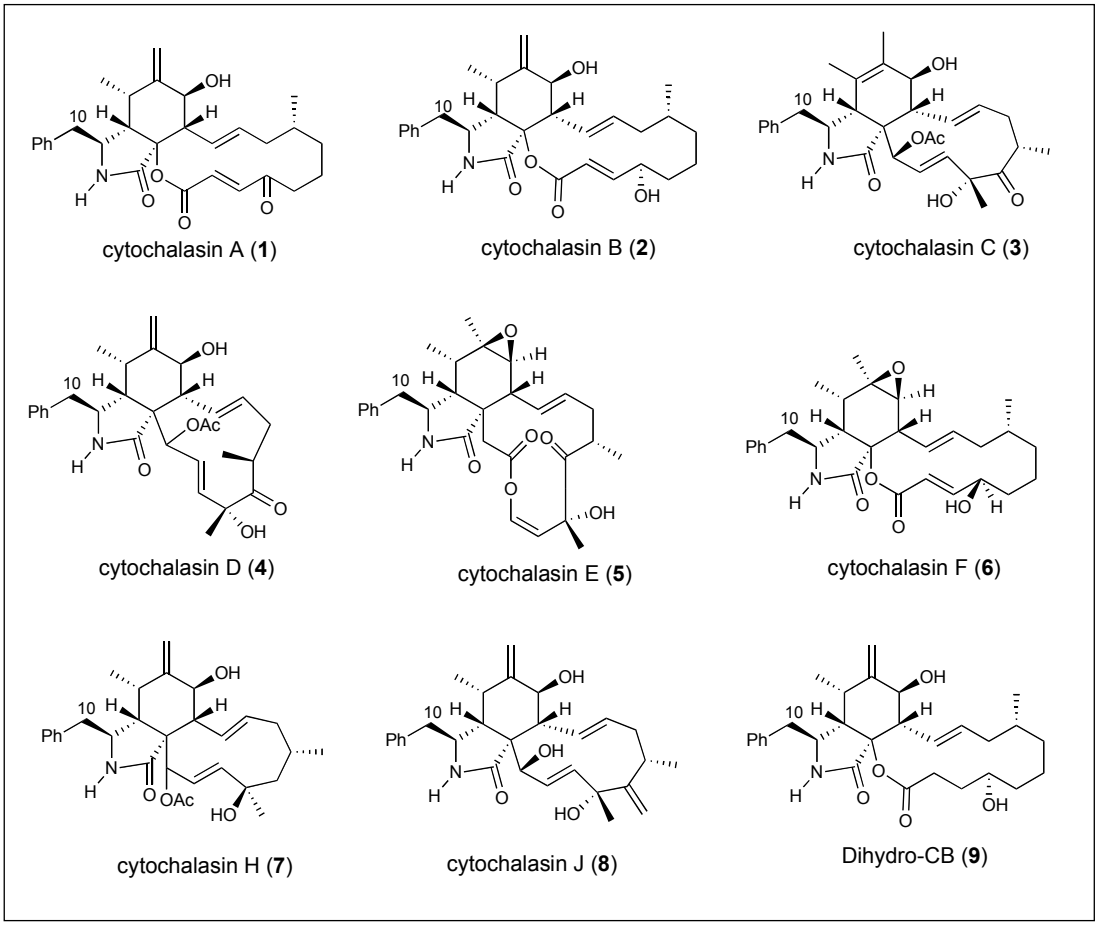


Figure 2-1 Examples of cytochalasans

The cytochalasans can be divided into three general groups based on whether they contain either an indole, phenyl or isopropyl moiety at position 10 of the perhydroisoindole ring system as shown in Figure 2-2. Those that contain an indole moiety are generally referred to as the chaetoglobosins (**10**). Cytochalasans containing phenyl and isopropyl moieties are referred to as cytochalasins (**3**) and aspochalasins (**11**) respectively[6] (Figure 2-2).

[6] (a) Cole, R.; Cox, R. H. *Handbook of toxic Fungal Metabolites*, Academic Press; New York, **1981**, 264-343; (b) Turner, W. B. *Fungal Metabolites*; Academic Press, New York, **1971**, pp 352; (c) Turner, W. B.; Aldridge, D. C. *Fungal Metabolites II*; Academic Press, New York, **1983**, pp 459; (d) Himes, R. H. *Biochim. Biophys. Res. Commun.* **1976**, *68*, 1362; (e) Fox, E. B.; Phillips, D. R. *Nature*, **1981**, 292.

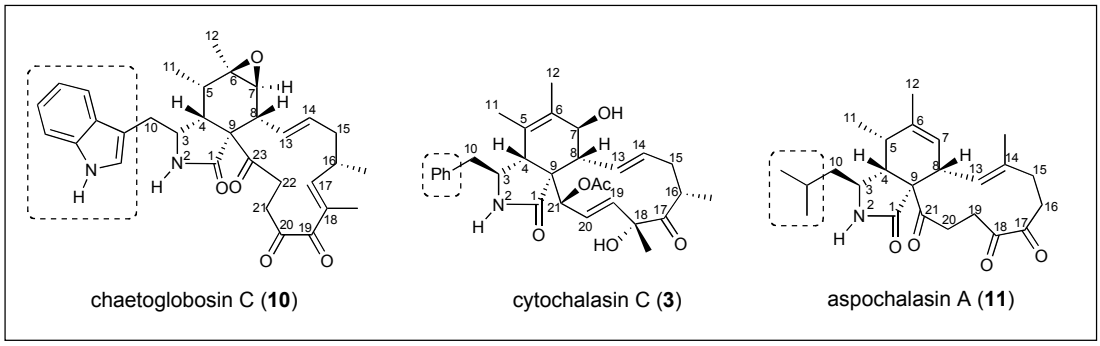


Figure 2-2 Types of cytochalasans

2.2 Biological Activities

Cytochalasans show a number of unusual, interesting and characteristic effects on the cell. It is known that cytochalasans generally possess distinctive biological effects including inhibiting the division of cytoplasm, reversible inhibition of cell movement, inducing nuclear extrusion,[7] inhibiting processes such as phagocytosis,[8] platelet aggregation, clot retraction,[9] glucose transport,[10] thyroid secretion[11] and release of growth hormone.[12] More recently, some of these compounds have been recognized for their potential as mycotoxins.[13]

[7] (a) Carter, S. B. *Nature* **1967**, *13*, 1985. (b) Krishan, A. *J. Cell Biol.* **1972**, *54*, 657. (c) Prescott, D. M.; Myerson, D.; Wallace, J. *Exp. Cell Res.* **1972**, *71*, 480. (d) Carter, S. B. *Endeavour* **1972**, *31*, 77.

[8] (a) Allison, A. C.; Davies, P.; De Petris, S. *Nature New Biol.* **1971**, *232*, 153. (b) Davis, A. T.; Estensen, R. D.; Quie, P. G. *Proc. Soc. Exp. Biol. Med.* **1971**, *137*, 161. (c) Axline, S. G.; Reaven, E. *J. Clin. Invest.* **1972**, *51*, 6a.

[9] (a) Shepro, D.; Belamarich, F. A.; Robblee, L. Chao, F. C. *J. Cell Biol.* **1970**, *47*, 544. (b) White, J. G. Roussel Conference on Platelet Aggregation, Masson, Paris, 4th March,**1971** (c) Haslam, R. J. *Biochem. J.* **1972**, *127*, 34P. (d) Majno, G.; Bouvier, C. A.; Gabbiani, G.; Ryan, C. B.; Statkov, P. *Thromb Diath. Haemorrh.* **1972**, *28*, 49.

[10] (a) Kletzien, R. F.; Perdue, J. F.; Springer, A. *J. Biol. Chem.* **1972**, *247*, 2964. (b) Mizel, S. B.; Wilson, L. *J. Biol. Chem.* **1972**, *247*, 4102. (c) Estensen, R. D.; Plagemann, P. G. *Proc. Nat. Acad. Sci. U.S.A.* **1972**, *69*, 1430.

[11] Williams, J. A.; Wolff, J. *Biochem. Biophys. Res. Commun.* **1971**, *44*, 422.

[12] (a) Schofield, J. G. *Nature New Biol.* **1971**, *234*, 215. (b) McPherson, M.A.; Schofield, J.G. *F.E.B.S. Lett.* **1972**, *24*, 45.

[13] Glinsukon, T.; Shank, R. C.; Wogan, G. N.; Newberne, P. M. *Toxical. Appl. Pharmacol.* **1975**, *32*, 135.

Cytochalasin A (**1**) is sulfhydryl-reactive, and was shown to inhibit growth and sugar uptake in a Saccharomyces strain.[14] Cytochalasin D (**4**) possesses antibiotic[15] and antitumor activities.[16] Cytochalasins H (**7**) and J (**8**) have been shown to have CNS activity.[17] Dihydrocytochalasin B (**9**) (dihydro-CB), the saturated derivative of Cytochalasin B (**2**), induces changes in morphology and motility, but has little effect on sugar transport.[18,19] Chaetoglobosins C shown cytotoxic to HeLa cells and chaetoglobosin K is a growth inhibitor of wheat colcoptiles.[6] Phomacins (eg. **13**), which are structurally related to aspochalasins, have been found to exhibit potent inhibitory activity against the HT29 colonic adenocarcinoma cell line[20] (Figure 2-3).

Since their commercial availability in the early 1970's, this group of compounds has become the subject of intense cytological research, which has led to the discovery of many new effects and a large number of synthetic cytochalasan derivatives. The literature abounds in reports and reviews of various aspects of their pharmacology.

[14] Kuo, S. -C.; Lampen, J. O. *Ann. N.Y. Acad. Sci.* **1974**, *235*, 137.
[15] Betina, V.; Micekova, D. *Z. Allg. Mikrobiol.* **1972**, *12*, 355; *Chem Abstr.* **1972**, *77*,160508q.
[16] Katagiri, K.; Matsuura, S. *J. Antifiot.* **1971**, *24*, 722.
[17] Kuo, S. -C.; Lampen, J. O. *Biochim Biophys. Acta* **1975**, *389*, 145.
[18] (a) Atlas, S. J.; Lin, S. *J. Cell Biol.* **1978**, *76*, 360; Lin, S.; Lin, D. C.; Flanagan, M. D. *Proc. Nat. Acad. Sci. U.S.A.* **1978**, *75*, 329. (b) Lin, S.; Spudich, J. A. *J. Biol. Chem.* **1974**, *249*, 5778.
[19] (a) Lin, D. C.; Lins, S. *J. Biol. Chem.* **1978**, *253*, 1415. (b) Rampal, A. L; Pinkovsky, H. B.; Jung, C. Y. *Biochemistry* **1980**, *19*, 679.
[20] Alvi, K. A.; Nair, B.; Pu, H.; Ursino, R.; Gallo, C.; Mocek, U. *J. Org. Chem.* **1997**, *62*, 2148.

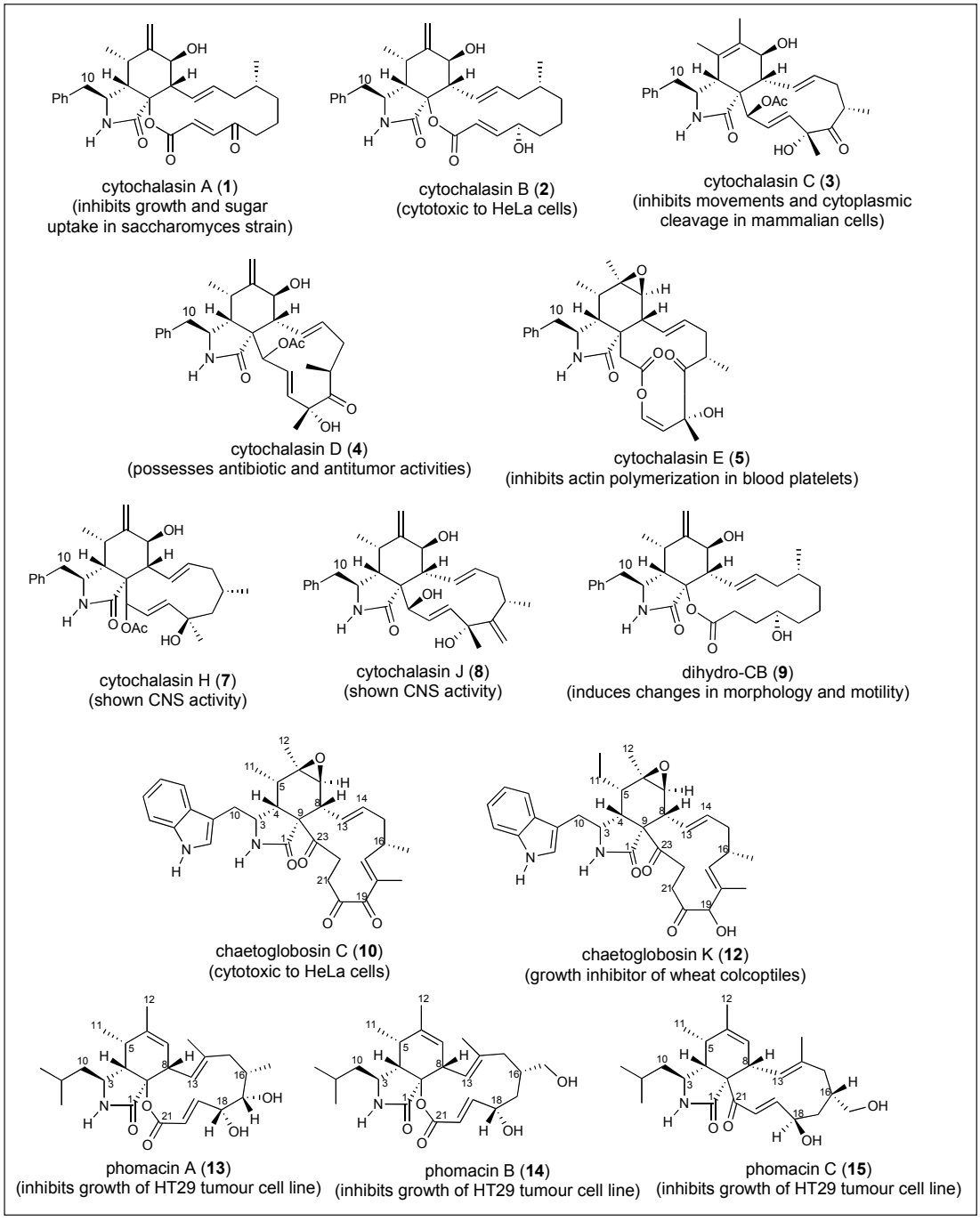


Figure 2-3[5,6,20]

[5] Carter, S. B. *Nature*, **1967**, *213*, 261.

[6] (a) Cole, R.; Cox, R. H. *Handbook of toxic Fungal Metabolites*, Academic Press; New York, **1981**, 264-343; (b) Turner, W. B. *Fungal Metabolites*; Academic Press, New York, **1971**, pp 352; (c) Turner, W. B.; Aldridge, D. C. *Fungal Metabolites II*; Academic Press, New York, **1983**, pp 459; (d) Himes, R. H. *Biochim. Biophys. Res. Commun.* **1976**, *68*, 1362; (e) Fox, E. B.; Phillips, D. R. *Nature*, **1981**, 292.

[20] Alvi, K. A.; Nair, B.; Pu, H.; Ursino, R.; Gallo, C.; Mocek, U. *J. Org. Chem.* **1997**, *62*, 2148.

2.3 Previous Synthetic Works

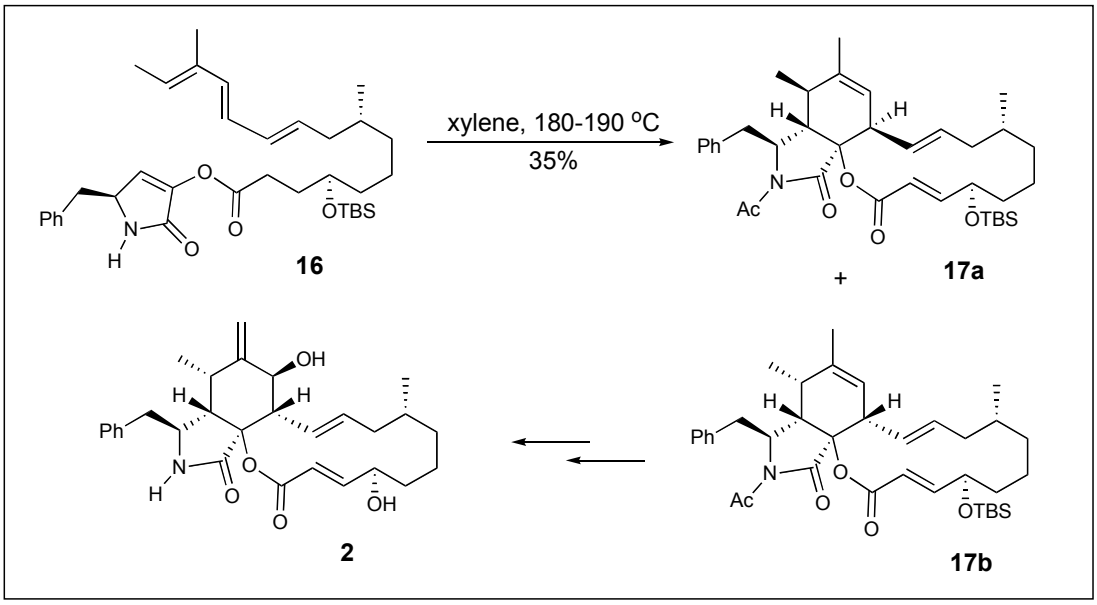
2.3.1 Introduction

Due to the unique biological activities and structural complexities of this group of compounds, cytochalasans have been the targets of much synthetic endeavors. The common strategies used in previous syntheses usually involved a thermal Diels-Alder reaction (either intermolecular or intramolecular) as the key step to form the six-membered core ring system together with the macrocyclic lactone or carbocyclic ring.

2.3.2 Literature Reviews

Stork and coworkers[21] synthesized cyctochalasin B (**2**) *via* intramolecular Diels-Alder reaction to construct the six-membered ring closure from tetraene **16** (Scheme 2-1). Tetraene **16** was heated at 180-190 °C using a base-washed, silylated, sealed tube for 6 d to give the cycloadducts **17**. The cycloadducts **17** were obtained as a 4:1 diastereomeric mixture where the major diastereomer was the desired product **17b**. The diastereomers were separated using column chromatography after deacetylation. Subsequent synthetic manipulations gave cytochalasin B (**2**).

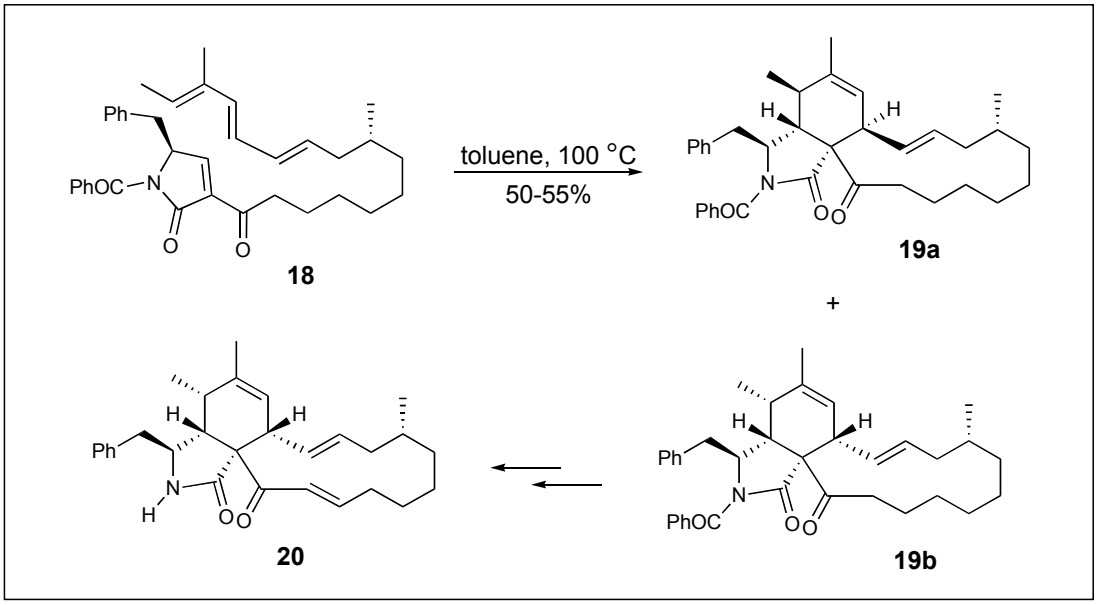
[21] Stork, G.; Nakamura, E. *J. Am. Chem. Soc.* **1983**, *105*, 5510.



Scheme 2-1

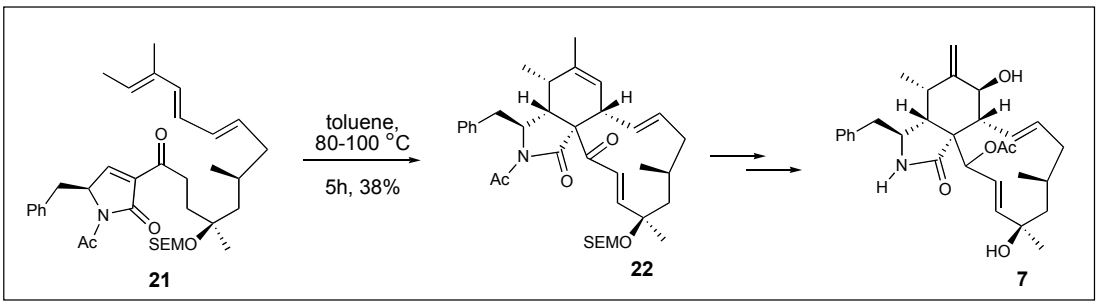
Using a similar path, Thomas *et. al*[22] carried out the intramolecular Diels-Alder reaction using a long chain triene-pyrrolinone **18** (Scheme 2-2). A solution of the triene **18** in toluene was heated in a sealed tube for 12 d to afford the product in 50-55% yield with a diastereomeric ratio of 52:48. The major isomer **19b** was the desired product. After a series of synthetic transformations, they completed the first total synthesis of proxiphomin **20**.

[22] (a) Thomas, E. J.; Tapolczay, D. J.; Whitehead, J. W. F. *J. Chem. Soc., Chem. Commun.* **1985**, *143*. (b) Thomas, E. J.; Whitehead, J. W. F. *J. Chem. Soc., Chem. Commun.* **1986**, 724.



Scheme 2-2

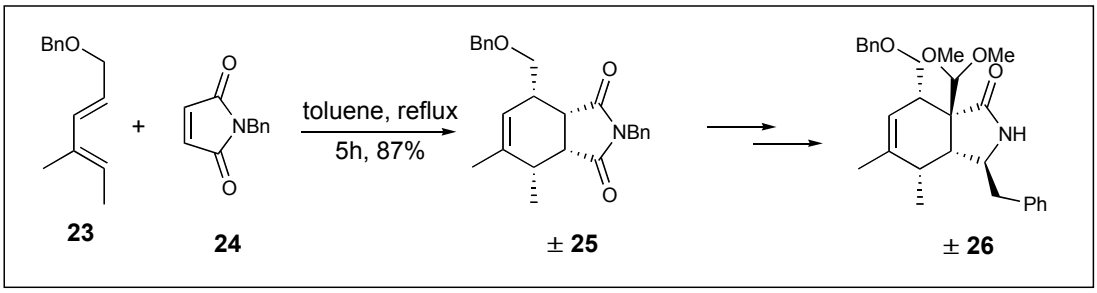
Four years later, Thomas *et al*[23] reported the synthesis of cytochalasin H (**7**) by using a similar approach as previous studies. Cyclization of the Diels-Alder precursor **21** was carried out by heating in toluene at 100 °C for 5h to give the desired cycloadduct **22**. Subsequent synthetic manipulations gave cytochalasin H (**7**) (Scheme 2-3).



Scheme 2-3

[23] (a) Thomas, E. J.; Whitehead, J. W. F. *J. Chem. Soc., Perk. Trans. I.* **1989**, 507; (b) Thomas, E. J.; Whitehead, J. W. F. *J. Chem. Soc., Perk. Trans. I.* **1989**, 519.

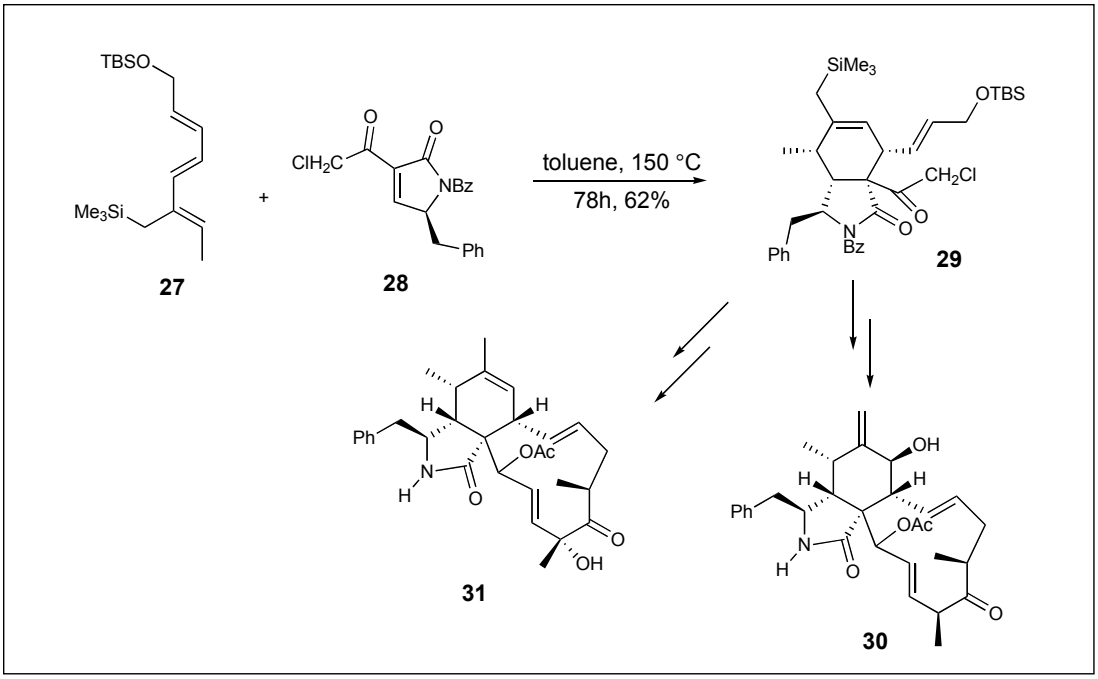
Hungate *et al*[24] synthesized the core ring structure of cytochalasans by a thermal intermolecular Diels-Alder reaction using diene **23** and a symmetrical dienophile **24**.[25] After cyclization, another seven steps were needed to give the racemic core ring structure **26** (Scheme 2-4).



Scheme 2-4

Vedejs *et al*[26] employed an intermolecular thermal Diels-Alder reaction in the total synthesis of cytochalasin D analogs **30** and zygoporin G (**31)** (Scheme 2-5). The reaction between triene **27** and a reactive dienophile **28** was carried out at room temperature to give a >15:1 mixture of the desired adduct **29**. The ring expansion strategy to incorporate the last four carbons of the 11-membered carbocycle was solved by using thioaldehyde technology. Cytochalasin D analogs **30** and zygoporin G (**31**) were synthesized in sixteen and thirteen steps from **29** respectively.

[24] Hungate, R. W.; Chen, J. L.; Starbuck, K. E.; Macaluso, S. A.; Rubino, R. S. *Tetrahedron Lett.* **1996**, *37*, 4113.
[25] Weinreb, S. M.; Starlett Jr., J. E.; Kim, Y. M. *J. Org. Chem.* **1981**, *46*, 5383.
[26] (a) Vedejs, E.; Reid, J. G. *J. Am. Chem. Soc.* **1984**, *106*, 4618; (b) Vedejs, E.; Rodgers, J. D.; Wittenberger, S. J. *J. Am. Chem. Soc.* **1988**, *110*, 4822; (c) Vedejs, E.; Rodgers, J. D.; Wittenberger, S. J. *J. Am. Chem. Soc.* **1990**, *112*, 4351.



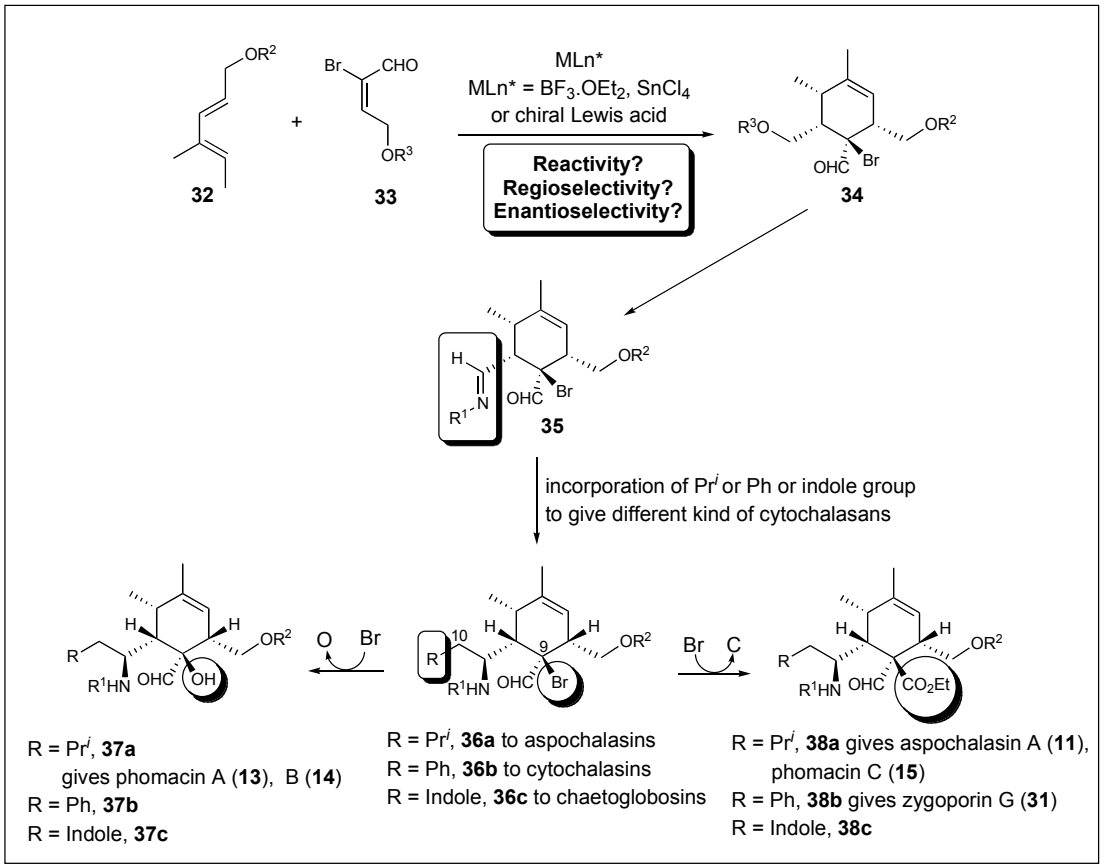
Scheme 2-5

All the reported syntheses of cytochalasans involved the use of thermal intramolecular or intermolecular Diels-Alder reaction as the key step, thus requiring harsh conditions which are difficult to carry out. These reported syntheses are long and required tedious synthetic manipulations. Besides, these methodologies cannot be employed with heat- or acid-sensitive compounds that are often featured in complex and multi-step syntheses.[27] Furthermore, the precursors needed for the cyclizations usually require activated dienophiles which are usually tedious to make or difficult to functionalize.

[27] Kobayashi, S.; Hachiya, I.; Takahori, T.; Araki, M.; Ishitani, H. *Tetrahedron Lett.* **1992**, *33*, 6815.

2.4 Our Synthetic Plan

Our strategy is to employ a Lewis acid catalyst and intermolecular Diels-Alder reaction to construct the six-membered ring. Lewis acid catalysts allow the reaction to proceed under mild conditions (at room temperature or below) with satisfactory yields. Reactions with less reactive dienes and dienophiles are also made possible, and the cycloaddition products are often highly regio- and stereo-selective. Furthermore, Lewis acids are capable of increasing both the reaction rate and selectivity, contrary to other catalyzed reactions where an increase in reaction rate is typically accompanied by a decrease in selectivity.[28]

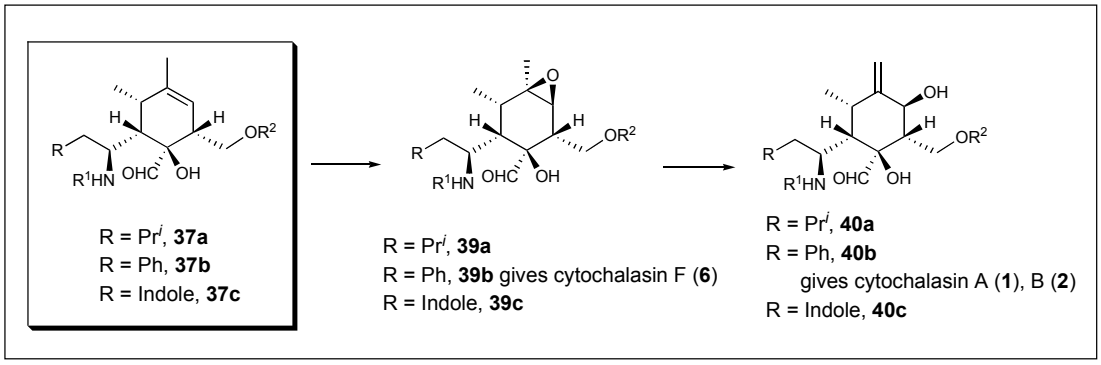


Scheme 2-6

[28] Fringuelli, F.; Taticchi, A. *The Diels-Alder Reaction Selected Practical Methods*, Wiley & Sons, England, **2002**, 99.

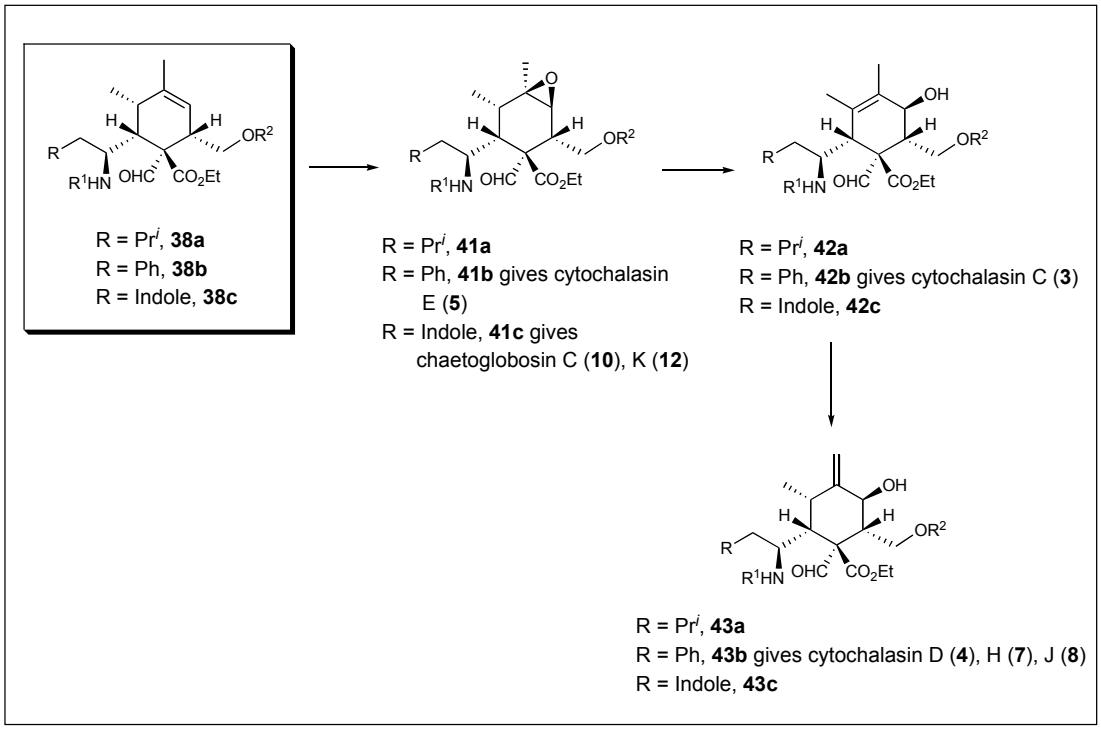
The key feature of our synthetic plan is the versatility of the key intermediates **35** as shown in Scheme 2-6. This versatile key intermediate **35** will allow us to synthesize almost all the known cytochalasans. The phenyl, isopropyl and indole groups can be incorporated from an imine containing functionality in intermediate **35** to afford key intermediates **36a**, **36b** and **36c** for the syntheses of aspochalasins, cytochalasins and chaetoglobosins respectively. The presence of bromide in the six-membered core ring system will enable us to introduce oxygen or carbon substituents in the C-9 position affording key intermediate **37a**, **37b**, **37c** and **38a**, **38b**, **38c** for the syntheses of cytochalasans with the macrocyclic lactone or carbocyclic rings (Scheme 2-6).

Further synthetic manipulations on the cyclohexane ring of **37a**, **37b** and **37c** will enable us to obtain the key intermediates for the syntheses of cytochalasin A (**1**), B (**2**) and F (**6**) (Scheme 2-7).



Scheme 2-7

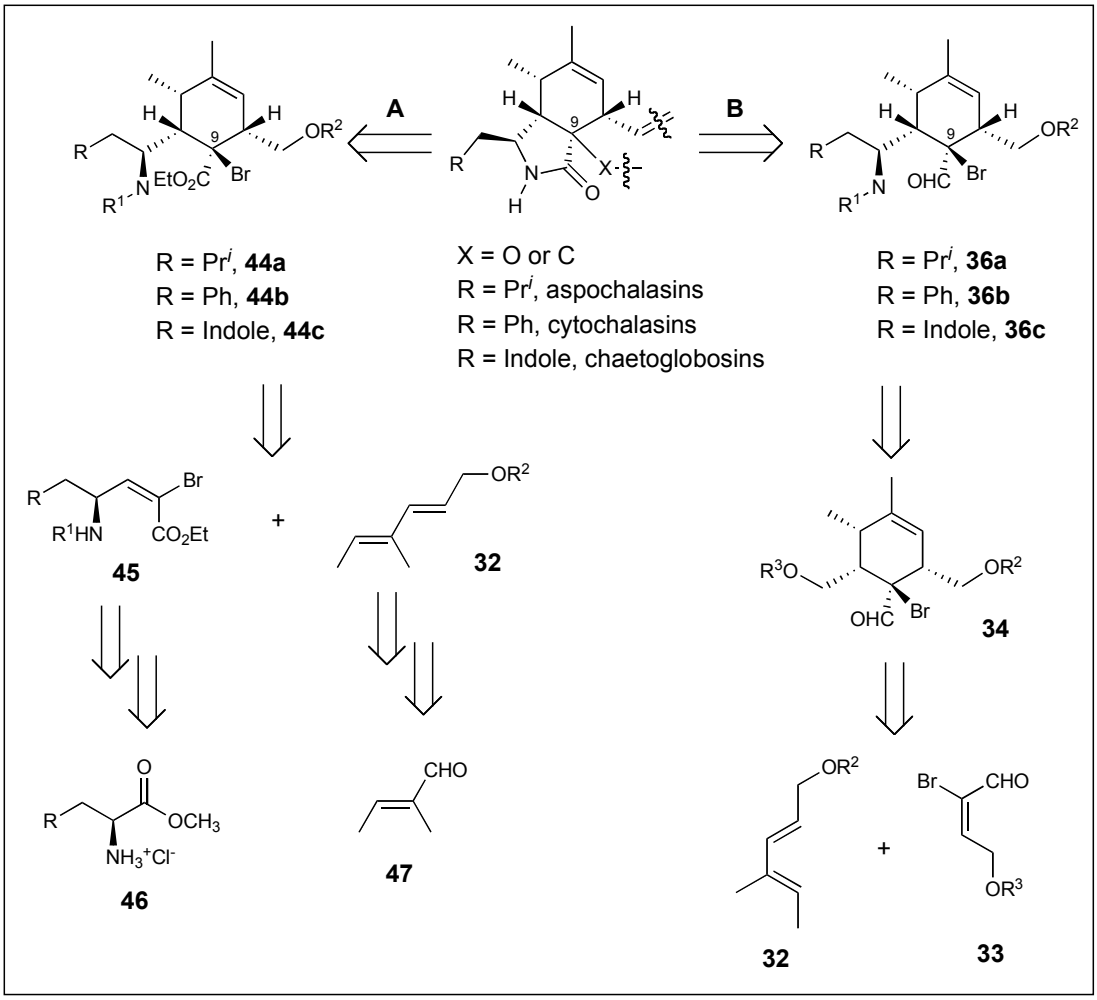
Similar strategy can be used on the cyclohexane ring of **38a**, **38b**, and **38c** to give the key intermediates for the syntheses of chaetoglobosin C (**10**) and K (**12**), cytochalasin C (**3**), D (**4**), E (**5**), H (**7**) and J (**8**) (Scheme 2-8).



Scheme 2-8

Two retrosynthetic approaches to cytochalasans are listed in Scheme 2-9. In both synthetic approaches, the cytochalasans are envisioned to arise from six-membered ring system with a bromide substituted at the C-9 position. The presence of bromide in the six-membered core ring system will enable us to introduce oxygen or carbon substituents in the C-9 position affording key intermediate for the syntheses of cytochalasans with the desired macrocyclic ring systems.

The main difference between the two approaches was on the substituents on the amine group. In approach A, the substituents on the amine group were incorporated in the diene's synthesis while in approach B, it was introduced in the later part of the synthesis (Scheme 2-9).

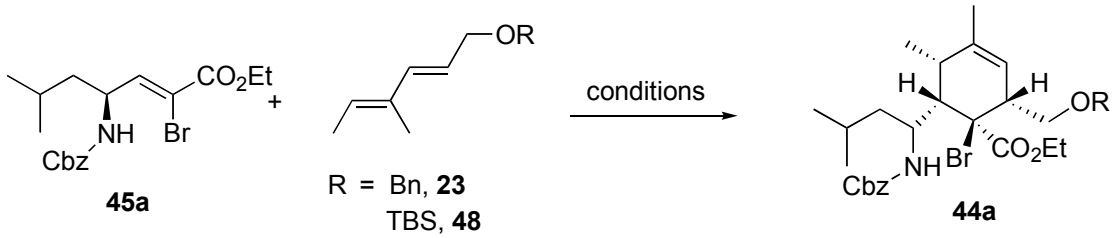


Scheme 2-9

In our previous synthetic studies towards the total synthesis of cytochalasans,[29] several Lewis acids catalyzed and thermal intermolecular Diels-Alder reaction using diene **23**, **48** and dienophile **45a** have been carried out, unfortunately, no cycloadduct was obtained (Table 2-1). It was also found that the ester functionality on dienophile **45a** is not sufficiently electron-withdrawing for promoting the Diels-Alder reactions and attempts to make the more reactive dienophile had failed. Since this approach did not yield any desired product, we discarded synthetic approach A and proceeded with synthetic approach B.

[29] Lim Zeyi, Honours thesis, **1998** - unpublished results.

Table 2-1

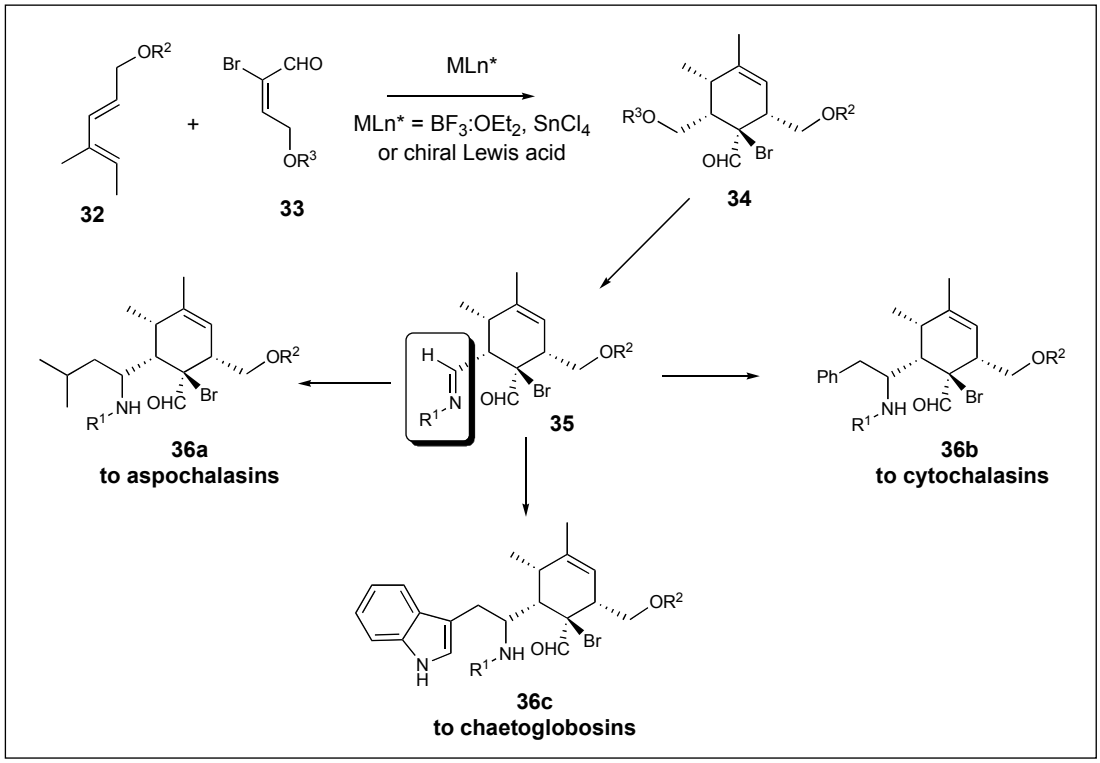


Entry	Dienes	Conditions	Yield
1	R = TBS	$In(OTf)_3$	No desired product, diene decomposed
2	R = Bn	$In(OTf)_3$	
3	R = TBS	$La(OTf)_3$	
4	R = Bn	$La(OTf)_3$	
5	R = TBS	$InCl_3$	
6	R = Bn	$InCl_3$	
7	R = TBS	$SnCl_4$	
8	R = Bn	$SnCl_4$	
9	R = TBS	$TiCl_4$	
10	R = Bn	$TiCl_4$	
11	R = TBS	Sealed tube Toluene, reflux	
12	R = Bn	Sealed tube Toluene, reflux	

2.4.1 Approach B

In our synthetic approach B, the substituents on the amine group are introduced in the later part of the synthesis. Thus, we envisaged that the phenyl, isopropyl and indole groups can be incorporated from an imine containing functionality in intermediate **35** to afford key intermediates **36a**, **36b** and **36c** for the

syntheses of aspochalasins, cytochalasins and chaetoglobosins respectively (Scheme 2-10). The use of a chiral Lewis acid[30] in the Diels-Alder reaction will enable us to control the relative as well as the absolute stereochemistry in the six-membered ring intermediate **34**.

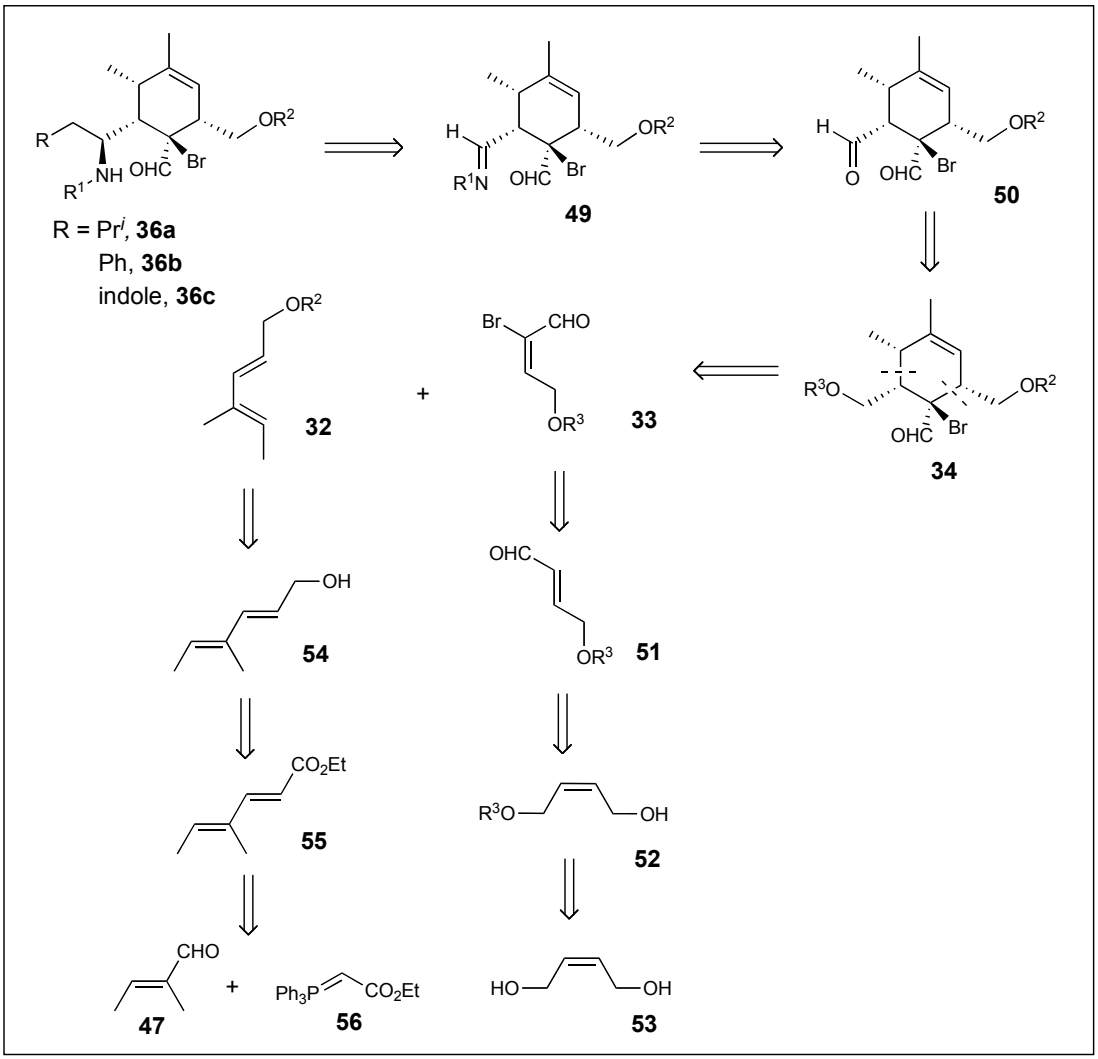


Scheme 2-10

Retrosynthetic analyses of key intermediates **36a**, **36b** and **36c** using a sequence of functional group interconversions leads to **34** *via* compound **49** and **50** (Scheme 2-11). Retrosynthetic disassembly of the six-membered ring system **34** provide diene **32** and dienophile **33**. It is projected that the construction of the six-membered ring could be achieved using Lewis acid catalyzed intermolecular Diels-Alder reaction between diene **32** and dienophile **33**.

[30] Loh, T. P.; Corey, E. J.; *Tetrahedron Lett*. **1993**, *34*, 3979.

Dienophile **33** can be derived from **51** *via* a bromination-elimination reaction, preceded with monoprotected alcohol **52** and finally from a commercially available *cis* 1,4-butendiol **53**. Meanwhile diene **32** can be obtained form tiglic aldehyde **47** and stabilized ylide **56**.



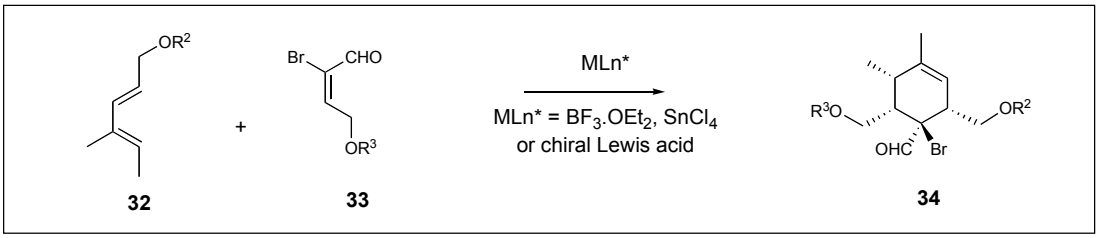
Scheme 2-11

Despite the dramatic improvements on the development of Diels-Alder technology for the construction of six-membered rings, the utility of Lewis acid-catalyzed intermolecular Diels-Alder reaction for the syntheses of complex molecules using open-chain dienes is not well established. This is probably due to the fact that

open-chain dienes are usually not very reactive in the Lewis acid-catalyzed intermolecular Diels-Alder reaction. In addition to that, the Lewis acid-catalyzed reaction does not work with acid-sensitive dienes and dienophiles. Therefore, there is still a need to develop more active catalysts (Lewis acids) which can effect this reaction for unreactive systems, such as those involving open-chain dienes.

2.5 Results and Discussions

Before attempting the Diels-Alder reaction on the real system of the molecule (Scheme 2-12), a model study was carried out using simple and commercially available dienes and dienophiles. Several Lewis acid-catalyzed conditions were applied and the results are showed in the following section.



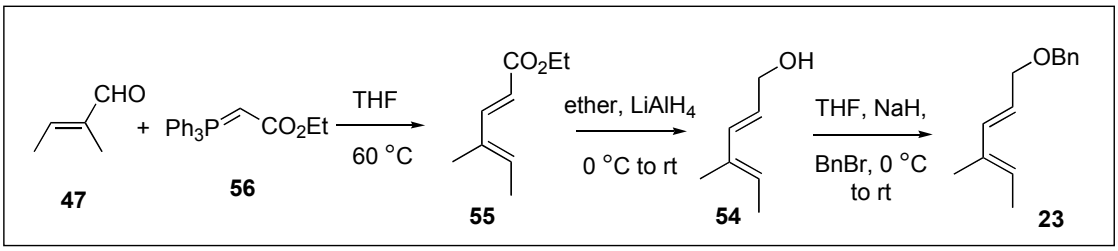
Scheme 2-12

2.5.1 Methodology Studies

With the plan in mind, we proceed to the syntheses of the diene and dienophiles in order to investigate the Diels-Alder reaction.

2.5.1.1 Synthesis of Diene 23

Synthesis of diene **23** was described in Scheme 2-13. Diene **23** was prepared in four steps from tiglic aldehyde (**47**). Treatment of **47** with carb(ethoxymethylene)triphenylphosphorane (**56**) in THF at 60 °C gave ester **55** in 93% yield. As expected, the *trans* isomer was the only product been isolated. When ester **55** was reduced using lithium aluminium hydride in ether at 0 °C, alcohol **54** was obtained in 92% yield. Protection of the alcohol functionality was carried out using benzyl bromide in the presence of sodium hydride in THF at 0 °C, giving the benzyl protected alcohol **23** in 83% yield.

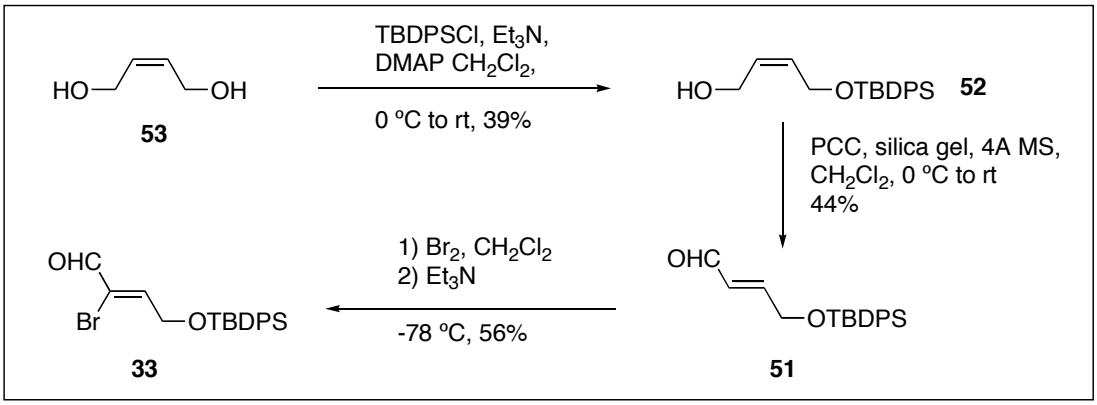


Scheme 2-13

2.5.1.2 Synthesis of Dienophile 51 and 33

Synthesis of dienophile **51** and **33** was carried out from a commercially available *cis* 1,4-buten-2-diol **53** (Scheme 2-14). Diol **53** was reacted with *t*-butyldiphenylsilylchloride (TBDPSCl) in the presence of triethylamine and DMAP in CH_2Cl_2 at 0 °C to give monoprotected alcohol **52** in 39% yield. Oxidation of alcohol **52** with pyridinium chlorochromate (PCC) in CH_2Cl_2 at 0 °C afforded dienophile **51** in 44% yield. Only the more stable *trans* isomer of dienophile **51** was obtained.

Further bromination of aldehyde **51** with bromine in CH_2Cl_2 followed by dehydrobromination by triethylamine at -78 °C gave dienophile **33** as a *cis*-isomer in 56% yield (Scheme 2-14).



Scheme 2-14

2.5.1.3 $In(OTf)_3$ Catalysed Diels-Alder Reaction in CH_2Cl_2

In the past few years, indium (III) complexes have been extensively used in organic synthesis as an efficient Lewis acid catalyst for various C-C bond formations and important transformations.[31] Especially noteworthy is indium triflate ($In(OTf)_3$) which our group is currently involved in exploiting its application in organic synthesis.

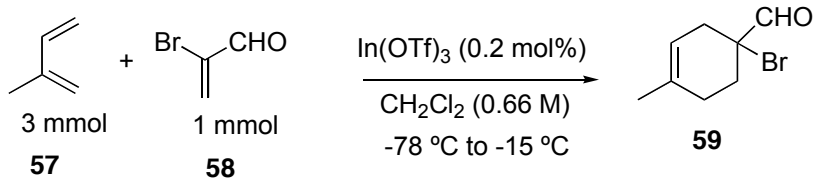
[31] For reviews, see: (a) Chauhan, K. K.; Frost, C. G. *J. Chem. Soc., Perkin Trans. 1*. **2000**, 3015. (b) Babu, G.; Perumal, P. T. *Aldrichim. Acta* **2000**, *33*, 16. For recent examples, see: (c) Mukaiyama, T.; Ohno, T.; Nishimura, T.; Han, J. S.; Kobayashi, S. *Chem. Lett.* **1990**, 2239. (d) Trost, B. M.; Sharma, S.; Schmidt, T. *J. Am. Chem. Soc*. **1992**, *114*, 7903. (e) Loh, T. -P.; Pei, J.; Cao, G. -Q. *J. Chem. Soc., Chem. Commun.* **1996**, 1819. (f) Loh, T. -P.; Pei, J.; Lin, M. *J. Chem. Soc., Chem. Commun*. **1996**, 2315. (g) Loh, T. -P.; Chua, G. -L.; Vittal, J. J.; Wong, M. -W. *J. Chem. Soc., Chem. Commun*. **1998**, 861. (h) Loh, T. -P.; Wei, L. -L. *Tetrahedron Lett*. **1998**, *39*, 323. (i) Loh, T. -P.; Huang, J. -M.; Goh, S. H.; Vittal, J. J. *Org. Lett.* **2000**, *2*, 1291. (j) Yang, J.; Li, C. -J. *Synlett* **1999**, 717. (k) Viswanathan, G. S.; Yang, J.; Li, C. -J. *Org. Lett.* **1999**, *1*, 993. (l) Ranu, B. C.; Jana, U. *J. Org. Chem*. **1998**, *63*, 8212. (m) Ranu, B. C.; Hajra, A.; Jana, U. *J. Org. Chem*. **2000**, *65*, 6270. (n) Ali, T.; Chauhan, K. K.; Frost, C. G. *Tetrahedron Lett.* **1999**, *40*, 5621. (o) Chauhan, K. K.; Frost, C. G.; Love, I.; Waite, D. *Synlett* **1999**, 1743. (p) Tsuchimoto, T.; Maeda, T.; Shirakawa, E.; Kawakami, Y. *J. Chem. Soc., Chem. Commun*. **2000**, 1573. (q) Gadhwal, S.; Sandhu, J. S. *J. Chem. Soc., Perkin Trans. 1*. **2000**, 2827.

Our group had published and described the $In(OTf)_3$-catalyzed conversion of γ-adduct homoallylic alcohol to its corresponding α-isomer through 2-oxonium [3,3]-sigmatropic rearrangement,[32] in the kinetic resolution reaction.[33] Recently, $In(OTf)_3$ was used in the preparation of a chiral catalyst with PYBOX as a ligand for a wide range of organic reactions such as allylation with aldehydes and ketones, and Mukaiyama-aldo reaction. High yields and enantiomeric excesses were reported.[34]

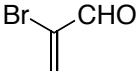
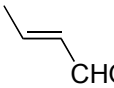
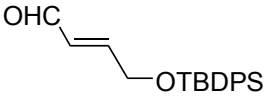
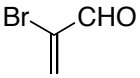
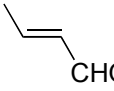
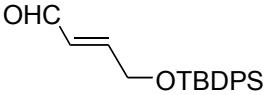
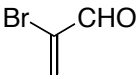
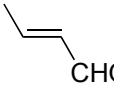
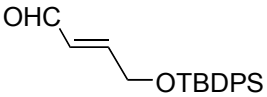
The preceding research prompted us to investigate the $In(OTf)_3$-catalyzed Diels-Alder reaction. In our initial experiment, isoprene (**57**) and bromoacrolein (**58**) were used as the substrates with $In(OTf)_3$ (0.2 equiv) as the catalyst, and CH_2Cl_2 (0.66 M) as the solvent. The reaction was first initiated at -78 °C and the reaction progress was monitored by TLC. No reaction occurred at -78 °C and upon slowly warming up the reaction mixture to -15 °C, the reaction proceeded and was complete after allowing the reaction to continue overnight. After reaction was completed, the Diels-Alder adduct was isolated in moderate yield. With this procedure, a series of dienes and dienophiles were investigated and the results are summarized in Table 2-2.

[32] Loh, T. -P.; Hu, Q. -Y.; Ma, L. -T. *J. Am. Chem. Soc.* **2001**, *123*, 2450-2451.
[33] Chen, S. -L.; Hu, Q. -Y.; Loh, T. -P. *Org. Lett.* **2004**, *6*, 3365-3367.
[34] (a) Lu, J.; Hong, M. -L.; Ji, S. -J.; Loh, T. -P. *Chem. Commun.* **2005**, 1010-1012. (b) Lu, J.; Ji, S. -J.; Teo, Y. -C.; Loh, T. -P. *Org. Lett.* **2005**, *7*, 159-161.

Table 2-2



3 mmol **57** + 1 mmol **58** → **59**

Diene	Dienophile (CHO)	Conditions	Yield
		CH_2Cl_2, -15 °C 24h	64%
		CH_2Cl_2, -15 °C 24h	64%
		CH_2Cl_2, -15 °C 24h	70%
		CH_2Cl_2, -15 °C 6d	77%
		CH_2Cl_2, -15 °C 24h	60%
		CH_2Cl_2, -15 °C 24h	68%
		CH_2Cl_2, -15 °C 24h	77%
		CH_2Cl_2, -15 °C 6d	69%
		CH_2Cl_2, -55 °C 14h	74%
		CH_2Cl_2, -78 °C	No desired product Polymerization occurred
		CH_2Cl_2, -78 °C	No desired product Polymerization occurred
		CH_2Cl_2, -78 °C	No desired product Polymerization occurred

2.5.1.4 $In(OTf)_3$ Catalyzed Diels-Alder Reaction in Ionic Liquid

Lately, a wide range of studies of Diels-Alder reaction in different reaction media has been extensively investigated, especially in matrices that are environmentally friendly as part of the general tend towards "Green Chemistry". One of the approaches is to use water instead of organic solvent as the reaction medium.[35] Recently, ionic liquids have attracted great interest among the synthetic organic chemists because they have been shown to have potential applications as environmentally friendly solvents in synthesis.[36] This is due to their interesting properties, notably their nonvolatile nature, non-flammability, reusability and insolubility in some solvents as well as their ability to dissolve catalysts.

Herein, we describe the indium triflate catalyzed Diels-Alder reactions between various dienes and dienophiles in ionic liquids. The reaction with the catalyst showed high *endo:exo* selectivity and only one regioisomer has been formed. It also gave good yields and the $In(OTf)_3$ can reused without losing its catalytic property.

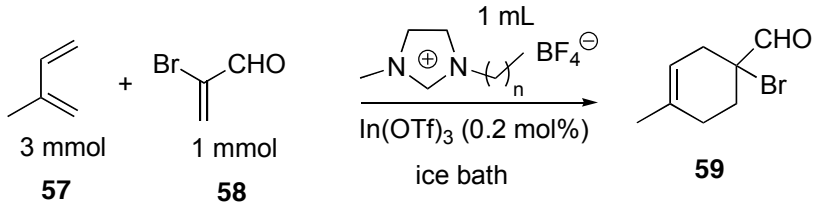
We initiated our Diels-Alder study by using isoprene (**57**) and bromoacrolein (**58**) as substrates in various types of ionic liquids. $In(OTf)_3$ (0.2 equiv) was added to the ionic liquid (1 mL) followed by bromoacrolein (**58**) (1 mmol) and isoprene (**57**) (3 mmol) in ice bath. After complete consumption of starting material (monitered by ^1H NMR), the reaction mixture was extracted with ether (15 mL x5) to leave the ionic liquid containing $In(OTf)_3$. The above procedure was used for a series of

[35] Loh, T. -P.; Pei, J.; Lin, M. *J. Chem. Soc., Chem Commun.* **1996**, 2315.

[36] (a) Wasserscheid, P.; Keim, W. *Angew. Chem. Int. Ed. Engl.* **2000**, *39*, 3772 and references cited therein; (b) Zhao, D. B.; Wu, M.; Kou, Y.; Min, E. *Catal. Today* **2002**, *74*, 157; (c) Sheldon, R. *Chem Commun.* **2001**, 2399 and references cited therein.

imidazolium-based ionic liquids. The results are summarized in Table 2-3. It was found that Diels-Alder reactions proceeded smoothly in [BF_4^-] and [PF_6^-] type ionic liquids to give the corresponding adducts in good yields. However, this procedure does not work for [Cl^-] type ionic liquid.

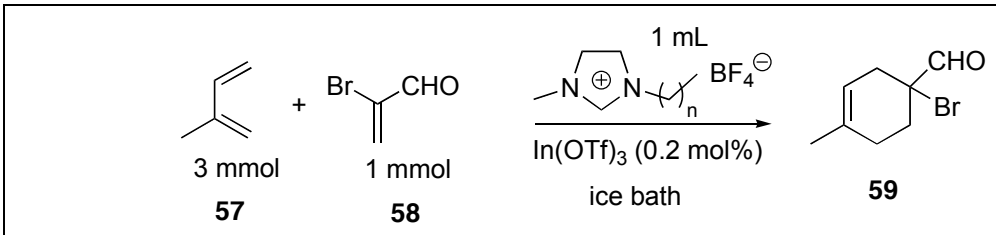
Table 2-3



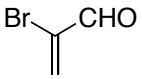
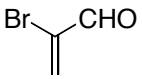
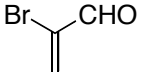
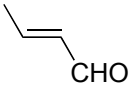
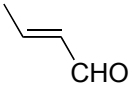
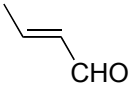
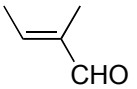
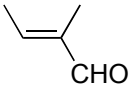
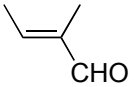
Ionic liquid	Yield (%)
[hmim][BF_4^-] , n = 5	79
[bmim][BF_4^-], n = 3	74
[hmim][PF_6^-] , n = 5	65
[hmim][PF_6^-] , n = 3	75
[hmim][Cl^-] , n = 5	5

With the use of [hmim][BF_4^-] as the reaction media, we proceeded with further investigation using various dienes and dienophiles. The results are shown in Table 2-4.

Table 2-4



3 mmol **57** + 1 mmol **58** → **59**

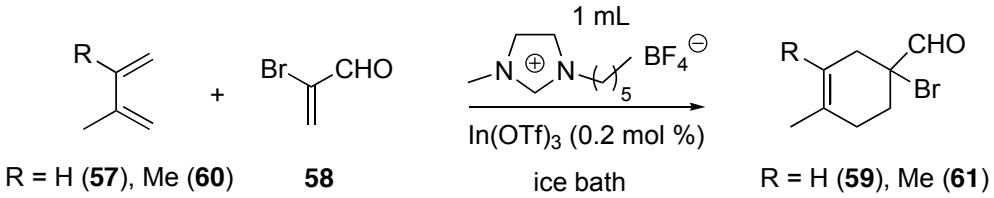
Diene	Dienophile	Yield (%)	*endo : exo*
		88	single regioisomer
		79	single regioisomer
		66	13 : 87
		46	single regioisomer
		77	single regioisomer
		52	89 : 11
		61	single regioisomer
		60	single regioisomer
		67	6 : 94

The *endo : exo* ratio of the aldehyde was determined using ^{1}H NMR spectroscopy.

With the successful of above reactions, we continued our study by exploring the recyclability of the catalyst. We carried out our study by using the reaction of isoprene and bromoacrolein in [hmim][BF_4^-] as a model study. After the reaction was

completed, the reaction mixture was extracted with ether (15 mL x5). The residue was concentrated, isoprene (**57**) and bromoacrolein (**58**) was added in and the reaction mixture was stirred in an ice bath. This process was repeated up to five times and it was found that the desired Diels-Alder adduct could still be obtained with comparable yields (Table 2-5).

Table 2-5



R = H (**57**), Me (**60**) **58** R = H (**59**), Me (**61**)

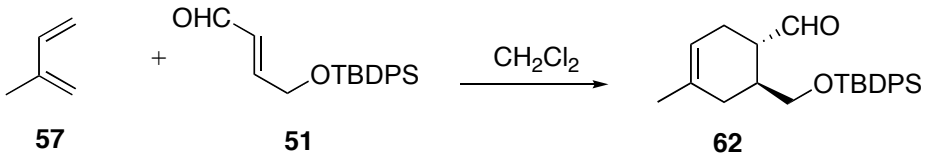

Times	Yield (%)	Yield (%)
1	79	88
2	71	76
3	64	80
4	66	85
5	63	-

In summary, indium triflate in ionic liquids had been found to be an efficient and reusable catalyst in Diels-Alder reactions. Furthermore, the use of the environmentally benign ionic liquids would further enhance the applicability of this procedure in the ever environmentally conscious manufacturing industry. Most importantly, since Diels-Alder reaction as one of the most powerful structural transformations in organic synthesis, this methodology will provide a useful entry into a wide range of natural products.

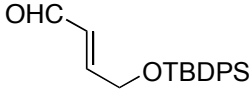
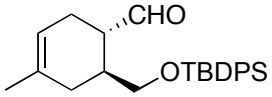
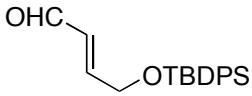
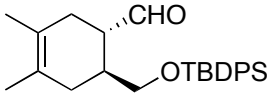
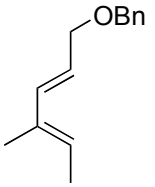
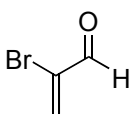
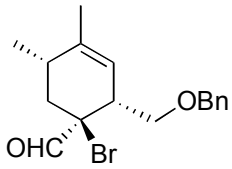
2.5.1.5 $BF_3.(OEt)_2$ Catalyzed Diels-Alder Reaction

Apart from the preceding study, we also explored the Diels-Alder reaction with several dienes and dienophiles using $BF_3.OEt_2$ as Lewis acid. A comparison between $BF_3.OEt_2$ and $In(OTf)_3$ was carried out and the results were summarized in Table 2-6.

Table 2-6



57 **51** **62**

Entry	Diene	Dienophile	Conditions	Product	Yield
1			$BF_3.OEt_2$ 0.5 equiv -78 to -60 °C 2d	 **62**	83%
2			$In(OTf)_3$ 0.5 equiv -15 °C 6d		77%
3			$BF_3.OEt_2$ 0.5 equiv -78 to -60 °C 2d	 **63**	75%
4			$In(OTf)_3$ 0.5 equiv -15 °C 6d		69%
5			$BF_3.OEt_2$ 0.5 equiv -78 to -60 °C 19h	 **64**	94%
6			$In(OTf)_3$ 0.5 equiv -15 °C 6d		68%

The Diels-Alder reaction was carried out successfully with both boron trifluoride diethyrate ($BF_3.OEt_2$) and indium triflate ($In(OTf)_3$) as catalysts, yielding the cycloadducts in moderately high yields. The regiochemistry and relative stereochemistry of the products were determined by NOESY spectroscopy. Results show that the conventional Diels-Alder reaction stereochemical outcome was followed, that is, the *endo* preference *via* the transition state shown in Figure 2-4.

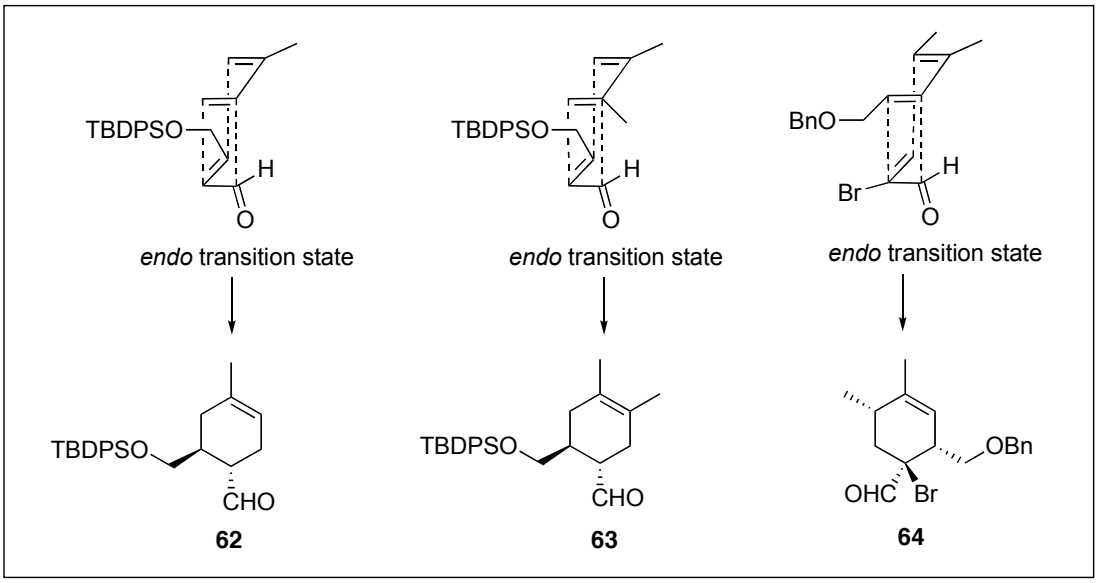


Figure 2-4

Having studied both Lewis acids as the catalyst for the Diels-Alder reaction in Table 2-6, we found that $BF_3.OEt_2$ gave better yields and shorter times compared to $In(OTf)_3$. Hence, we initiated the investigation of the Diels-Alder reaction using $BF_3.OEt_2$ as the Lewis acid with diene **23** and dienophiles **51** and **33**. We start the reaction at low temperature (-78 °C). However, no reaction occurred when we monitored with TLC. Thus, we warm up the reaction slowly to -20 °C. No desired product was observed from the reaction mixture but the diene **23** was decomposed

slowly. Even with increased amounts of diene **23** used to compensate for its decomposition, the desired product was not obtained.

Other Lewis acids were also been studied with this reaction system (Table 2-7). They are $SnCl_4$, $AlCl_3$, $In(OTf)_3$ and $Sm(OTf)_3$ were tried. It was found that the diene decomposed even under mildly acidic condition. Hence, slightly milder Lewis acids such as MacMillan's catalysts[37] were employed but no desired product were obtained (entry 11 and 12). The thermal condition was also employed to this reaction system (entry 13 and14). Same as others entries, no product was obtained but resulted in the decomposition of diene **23**.

Since the proposed dienophiles **51** and **33** does not yield the desired cycloadduct, other alternatives were explored. One of the alternatives is to synthesis a very reactive dienophile which can be applied to our system.

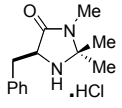


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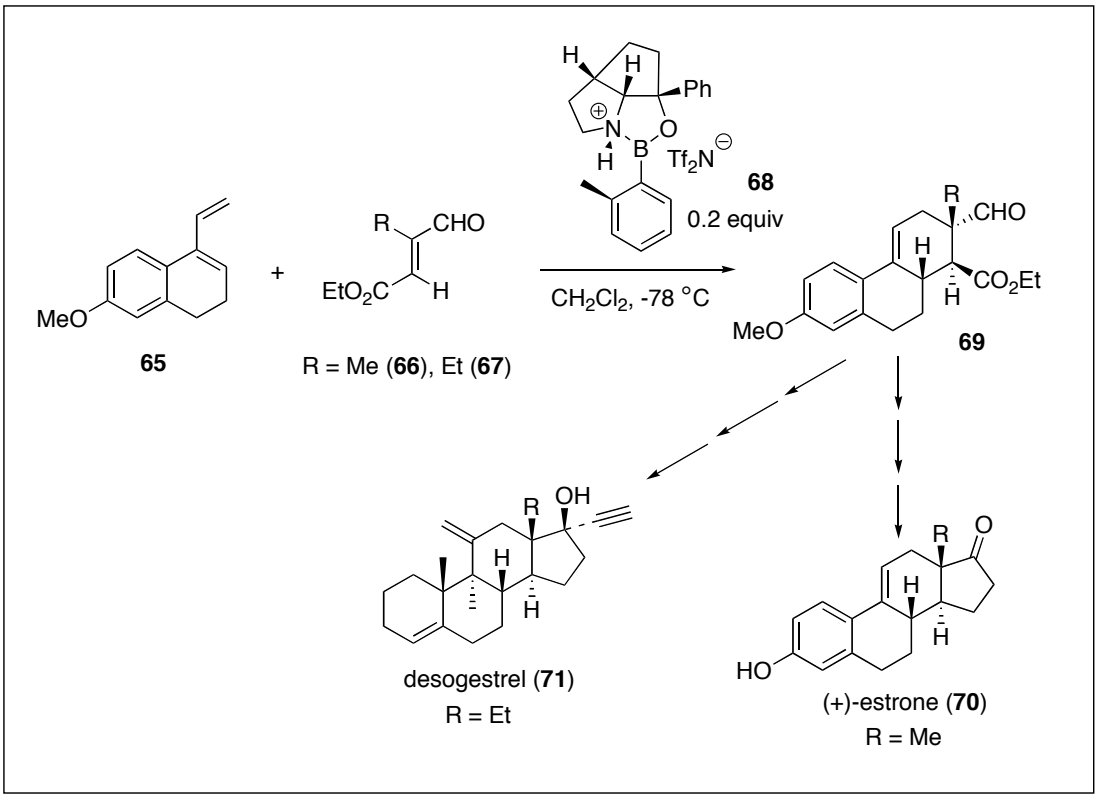
Table 2-7

23 R = Br (**33**); H(**51**) **34**

Entry	Dienophile	Conditions	Yield
1	R = H	$BF_3.OEt_2$ (0.5 to 1 equiv) CH_2Cl_2 -78 °C to -20 °C	Diene decomposed
2	R = Br	$BF_3.OEt_2$ (0.5 to 1 equiv) CH_2Cl_2 -78 °C to -20 °C	Diene decomposed
3	R = H	$SnCl_4$ (0.5 to 1 equiv) CH_2Cl_2 -78 °C to -20 °C	Diene decomposed
4	R = Br	$SnCl_4$ (0.5 to 1 equiv) CH_2Cl_2 -78 °C to -20 °C	Diene decomposed
5	R = H	$AlCl_3$ (0.5 to 1 equiv) CH_2Cl_2 -78 °C to -20 °C	Diene decomposed
6	R = Br	$AlCl_3$ (0.5 to 1 equiv) CH_2Cl_2 -78 °C to -20 °C	Diene decomposed
7	R = H	$In(OTf)_3$ (0.2 to 1 equiv) CH_2Cl_2, -20 °C	Diene decomposed
8	R = Br	$In(OTf)_3$ (0.2 to 1 equiv) CH_2Cl_2, -20 °C	Diene decomposed
9	R = H	$Sm(OTf)_3$ (0.2 to 1 equiv) CH_2Cl_2, -10 °C	Diene decomposed
10	R = Br	$Sm(OTf)_3$ (0.2 to 1 equiv) CH_2Cl_2, -10 °C	Diene decomposed
11	R = H	MacMillan catalysts (0.2 to 1 equiv) $CH_3CN:H_2O$, rt	No reaction
12	R = Br	MacMillan catalysts (0.2 to 1 equiv) $CH_3CN:H_2O$, rt	No reaction
13	R = H	Sealed tube Toluene, K_2CO_3	Diene decomposed
14	R = Br	Sealed tube Toluene, K_2CO_3	Diene decomposed

2.5.2 Application of Model Study Towards the Syntheses of the Six-Membered Rings in Cytochalasans

Recently, Corey's group[38] reported that aldehyde-esters **66** and **67** are good dienophile in the synthesis of estrone **70** and desogestrel **71**. The reaction was carried out using Dane's diene **65** and aldehyde-esters **66** and **67**. High yield and enantiomeric excess (scheme 2-15) was obtained. Hence, we went on to try this aldehyde-ester in our synthetic plan.

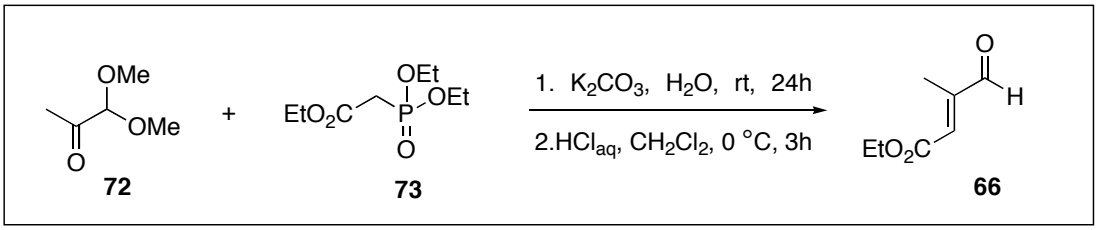


Scheme 2-15

[38] (a) Hu, Q. -Y.; Rege, P. D.; Corey, E. J. *J. Am Chem. Soc.* **2004**, *126*, 5984-5986. (b) Hu, Q. -Y.; Zhou, G.; Corey, E. J. *J. Am Chem. Soc.* **2004**, *126*, 13708-13713.

2.5.2.1 Synthesis of dienophile 66

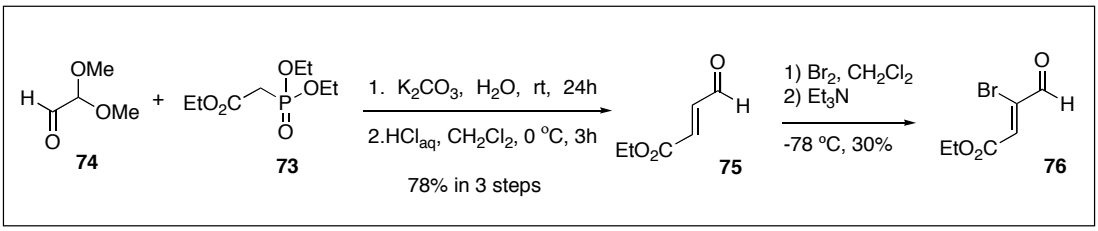
Dienophile **66** was prepared in 83% yield by Horner-Emmons reaction of commercially available 1,1-dimethoxyacetone (**72**) and ethyl 2-(diethoxyphosphoryl) acetate (**73**) followed by acid hydrolysis with 3N HCl-CH_2Cl_2 at 0 °C for 3h. (Scheme 2-16)



Scheme 2-16

2.5.2.2 Synthesis of dienophile 75 and 76

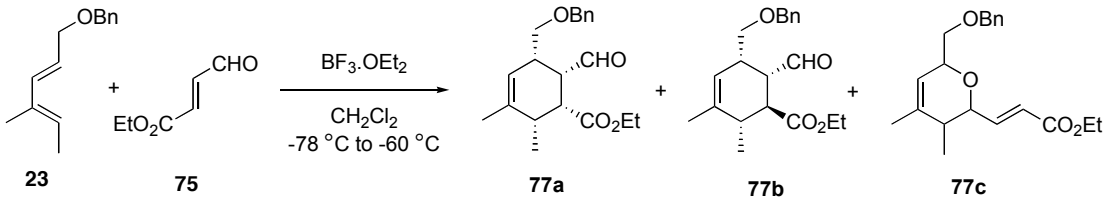
Dienophile **75** was prepared in 78% yield by Horner-Emmons reaction of commercially available 1,1-dimethoxyacetaldehyde (**74**) and ethyl 2-(diethoxyphosphoryl) acetate (**73**), followed by acid hydrolysis with 3N HCl-CH_2Cl_2 at 0 °C for 3h. Further bromination of aldehyde **75** with bromine in CH_2Cl_2 followed by dehydrobromination by triethylamine at -78 °C gave dienophile **76** as a *cis*-isomer in 30% yield (Scheme 2-17).



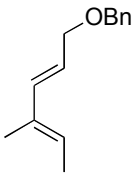
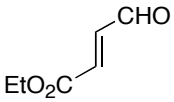
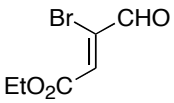
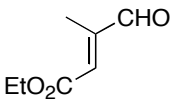
Scheme 2-17

With regards to Diels-Alder reactions using multifunctional diene and dienophile, less reactive diene and dienophile may not yield the desired results. On the other hand, multifunctional diene and dienophile such as ours have not been widely studied in Diels-Alder cycloaddition in the presence of Lewis acid. Since Lewis acid $BF_3.OEt_2$ afforded better result of the cycloaddition as compared to $In(OTf)_3$ (Table 2-6, section **2.5.1.5**), we thus used $BF_3.OEt_2$ for further studies. A series of aldehyde-ester were tested and the results are shown in Table 2-8. Two competing reactions; [4 + 2] cycloaddition and hetero Diels-Alder were observed during this study.

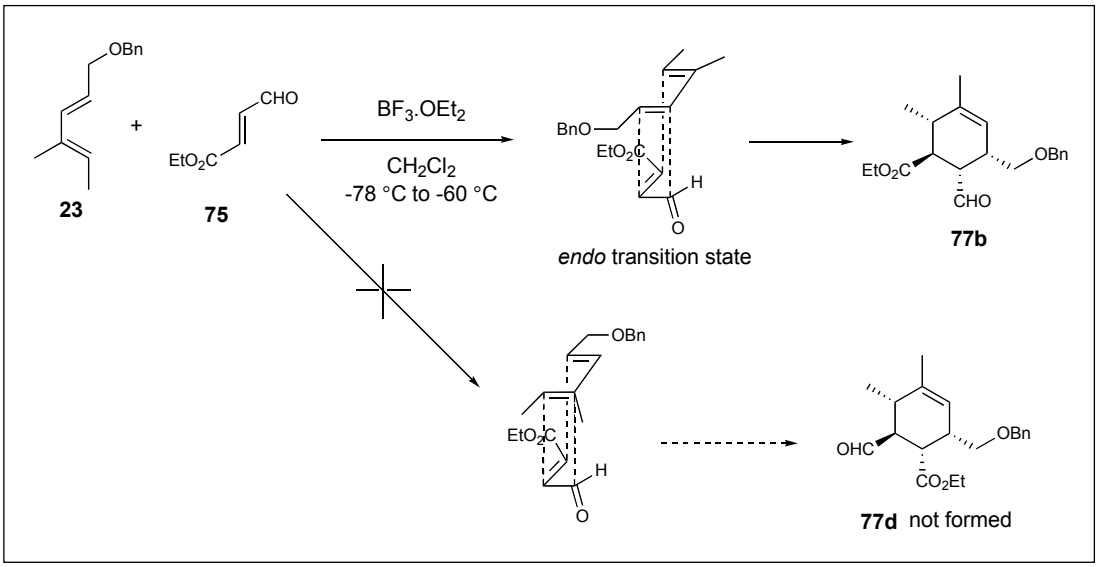
Table 2-8



23 **75** **77a** **77b** **77c**

Diene	Dienophile	Yield (%)	Ratio a : b : c
 **23**		82	0 : 1 : 1
		56	Only **c** observed
		23	Only **c** observed

The regiochemistry and relative stereochemistry of the cycloadduct **77b** was as shown in Figure 2-5. The stereochemistry of the products suggests that due to secondary orbital interaction, the Diels-Alder reaction had proceeded by an *endo* transition state to give product **77b** (Scheme 2-18).



Scheme 2-18

The relative stereochemistry of cycloadduct **77b** was confirmed by NOESY experiment showing the interaction between corresponding protons (Figure 2-5). We are unable to observe the interaction between H-6 and H-1 due to the overlapping between the two protons. By using 1D and 2D NMR experimental data, we concluded that H-5 and H-6 are in the *anti* configuration.

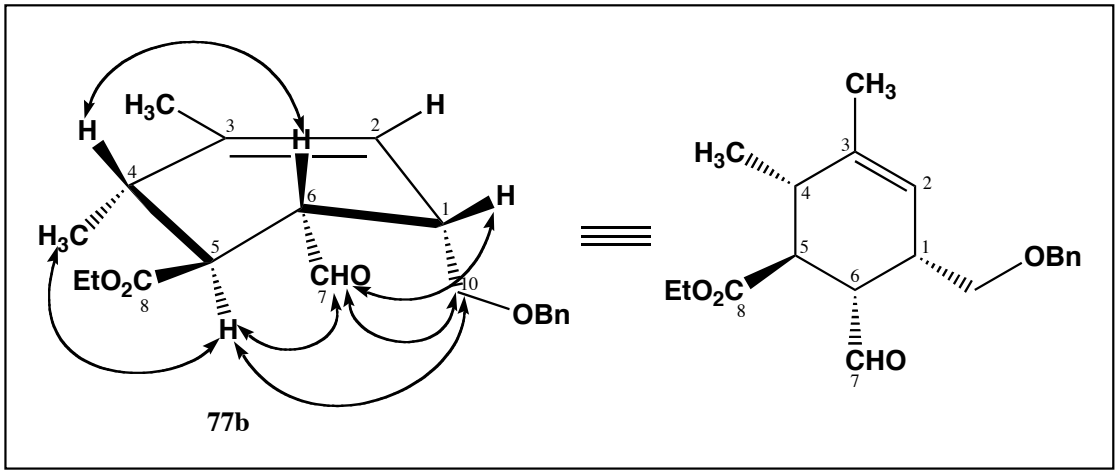
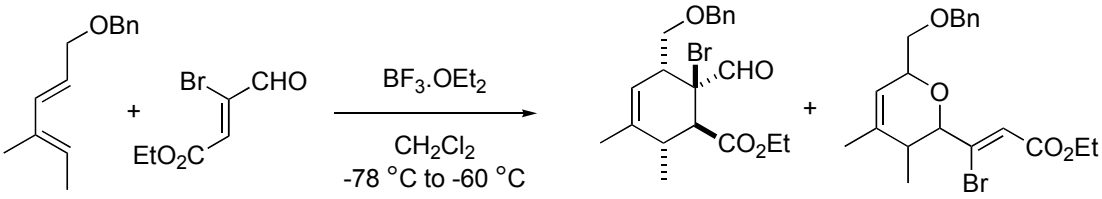


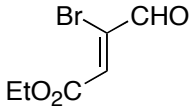
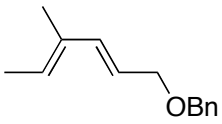
Figure 2-5

While seeking to access this aldehyde-ester in our synthetic plan, a study was conducted on aldehyde-ester **76** with a series of dienes and the results are shown in Table 2-9. As predicted, the product obtained depends on the reactivity of the diene used. Reactive diene such as cyclopentadiene (entry 3) give rise to normal cycloadduct only, whereas uncreative diene **23** (entry 4) gave rise to heteroadduct as the only product. Expectedly, 2,3-dimethyl butadiene (entry 1) and isoprene (entry 2) produced a mixture of normal and hetero Diels-Alder product.

Table 2-9



23 **76** **78b** **78c**

Entry	Diene	Dienophile	Yield (%)	Ratio b : c	Reactivity
1			95	1 : 2	2nd
2			58	1 : 8	3rd
3			72	Only **b** observed	1st
4			56	Only **c** observed	4th

Even though we managed to construct the cyclohexane ring **77b** (Scheme 2-19), the stereochemistry at C_5 was not the desired one (Figure 2-6). It appears that CHO and CO_2Et functionalities should be at the same side instead of the *anti*-position. *Anti* dienophile will leading to the undesired cycloadduct during the Diels-Alder reaction.

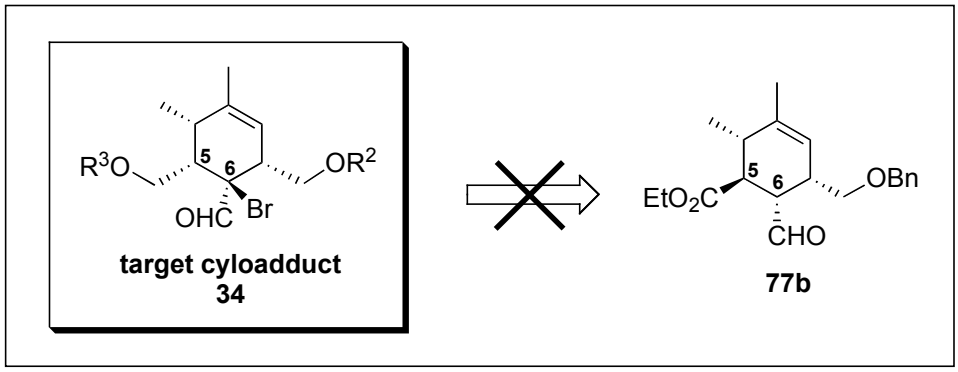
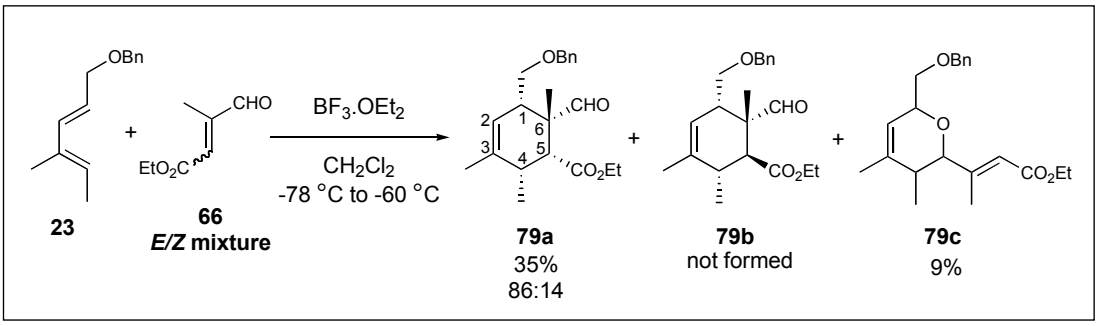


Figure 2-6

In order to obtain the correct cycloadduct to carry on the cyctochalasans synthesis, our next approach is to synthesize the *syn* dienophile, where the CHO and ester are at the same side. Firstly, we examined the *E* and *Z* mixture (4:1) of dienophile **66** with diene **23** in the presence of $BF_3.OEt_2$ and CH_2Cl_2 as solvent at -60 °C for overnight. Cycloadduct **79a** was isolated in 35% yield from the crude mixture (Scheme 2-19). After NMR study, we found that the stereochemistry on C_5 was in the correct form. The cycloadduct **79a** also proceeded by an *endo* transition state (will discuss in section **2.5.2.3**).



Scheme 2-19

With cycloadduct **79a** in hand, we still need to carry some problems. One of the major problems is that the methyl group at C_6 was very difficult to functionalized to the proposed compound as mention in our retroanalysis plan (Figure 2-7). To overcome this problem, we plan to make the more elegant dienophile which can be applied to our system. Our initial attempt was to make the dialdehyde **80** as shown in Figure 2-7. However, no desired product was obtained. So, we changed our focus to aldehyde-diester **81**. The procedure is described in following section.

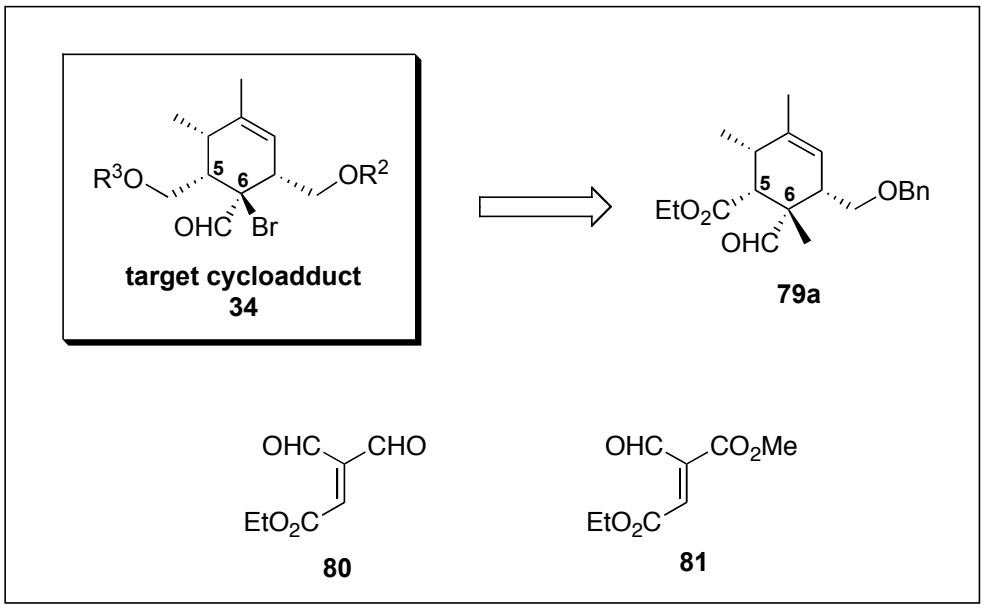
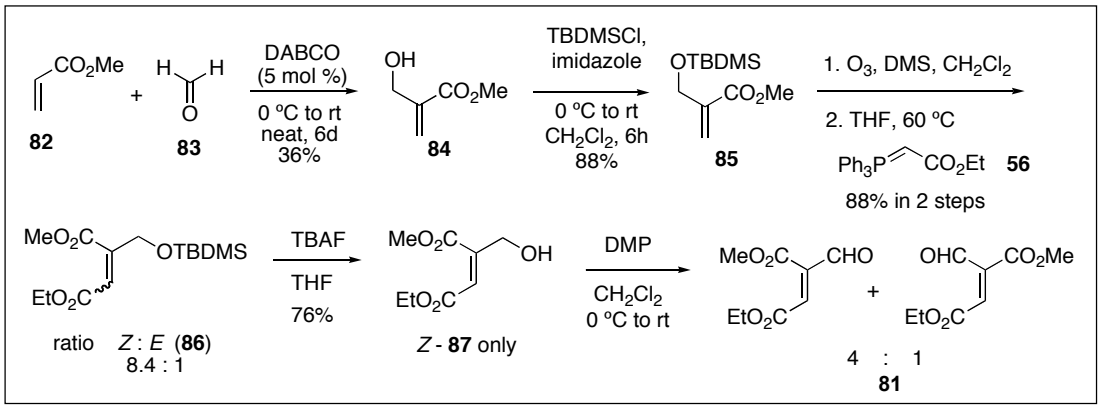


Figure 2-7

2.5.2.3 Synthesis of Dienophile 81

Synthesis of dienophile **81** was completed in 6 steps from the commercially available formadehyde **83** and methyl acrylate **82** (Scheme 2-20). Alcohol **84** was prepared by Baylis Hilman reaction between formaldehyde **83** and methyl acrylate **82** in the presence of a catalytic amount of DABCO. Protection of alcohol **84** with TBDMSCl and pyridine in CH_2Cl_2 gave the protected alcohol **85** in 88% yield. Ozonolysis followed by Wittig reaction with a stabilized ylide **56** afforded 88% yield of α, β-unsaturated ester **86** in two steps. The silicon protecting group was removed and oxidized to the corresponding aldehyde **81**. Since the aldehyde **81** is very unstable, it was directly used for the Diels-Alder reaction without any further purification.



Scheme 2-20

From the NMR studies (NOE) on **86**, **87** and **81** (Figure 2-8), we found that the main product obtained from the Wittig reaction gave the (*Z*)-isomer. After desilylation, alcohol **87** was obtained as a single isomer, which is the (*Z*) configuration. The desired (*E*)-isomer was only obtained as a minor product during

the DMP oxidation when the isomerization occurred. The NMR shown two aldehyde peaks at 9.65 ppm and 10.16 ppm which correspond to *Z* and *E* isomer respectively.

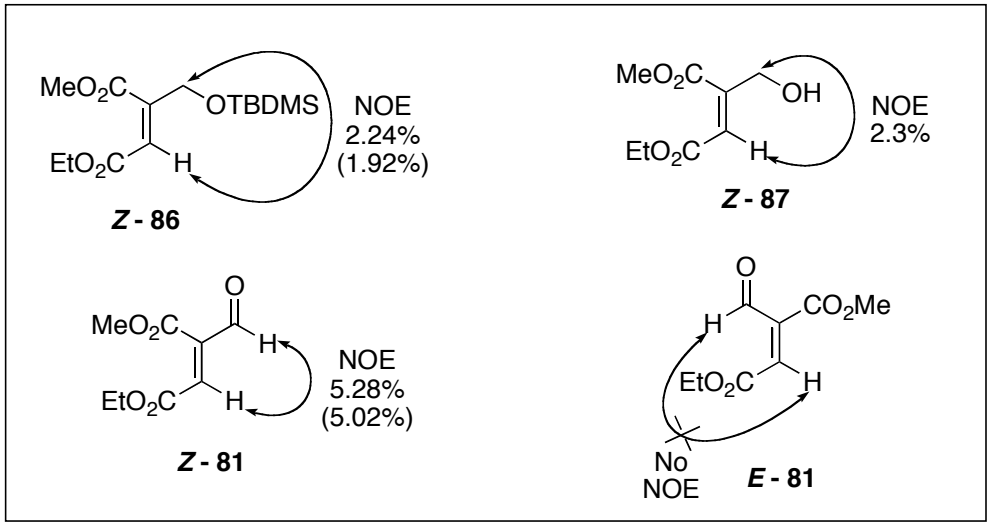
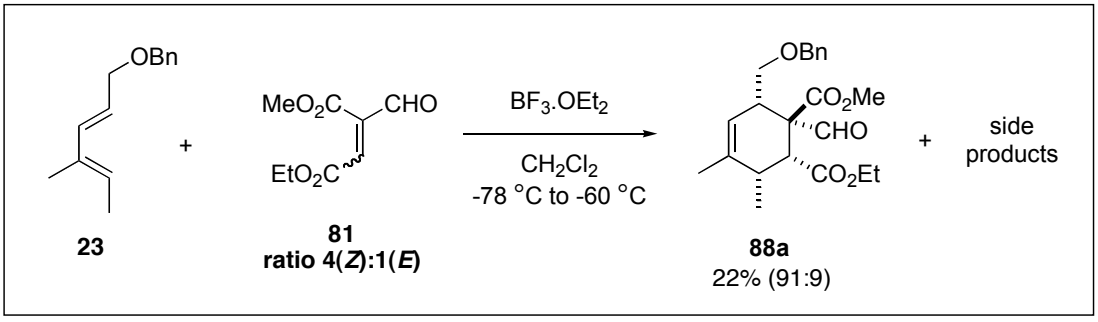


Figure 2-8

When we treated the crude aldehyde **81** and diene **23** with $BF_3.OEt_2$ in dichoromethane, we obtained cycloadduct **88a** as colorless oil in 22% yield after 16h of reaction at -60 °C (Scheme 2-21). We found that besides our desired cycloadduct **88a**, some other side products also formed in the reaction mixture.

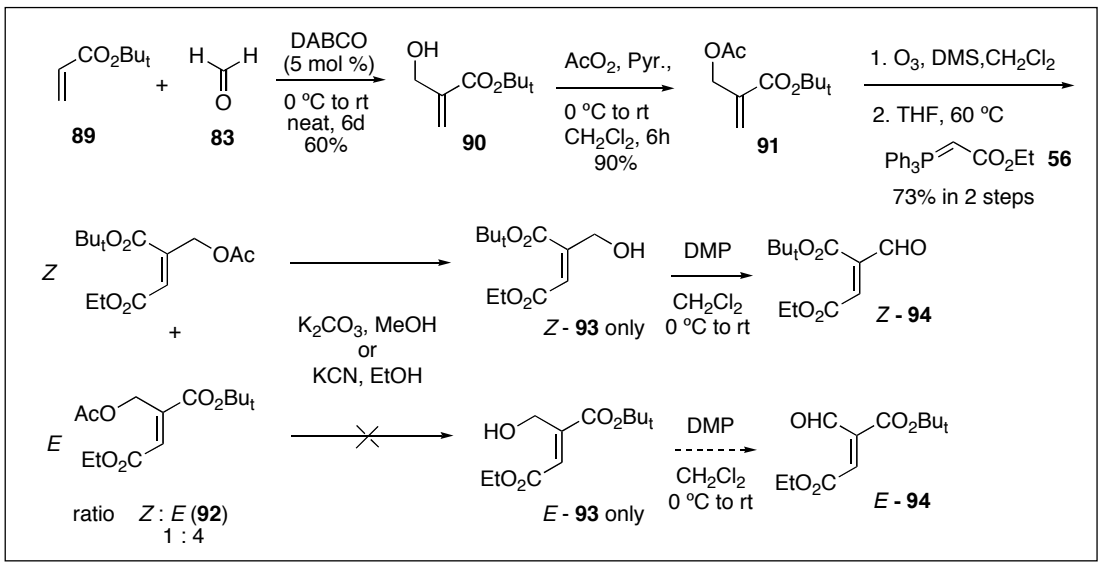


Scheme 2-21

Since our desired dienophile is (*E*)-isomer **81**, we needed to seek for other alternatives in order to carry on this synthesis. One of the alternatives is to change the methyl ester to *t*-butyl ester. We expect that the steric hindrance provided by the bulky *t*-butyl group would give the desired (*E*)-isomer as the major product.

2.5.2.4 Synthesis of Dienophile 94

Efforts to synthesis the (*E*)-isomer was carried out as shown in Scheme 2-22. Alcohol **90** was prepared by a Baylis-Hilman reaction between formadehyde **83** and *t*-butyl acrylate **89** in the presence of a catalytic amount of DABCO. Protection of the alcohol **90** was carried out with acetic anhydride with pyridine in CH_2Cl_2, giving the protected alcohol **91** in 90% yield. Ozonolysis followed by Wittig reaction with a stabilized ylide **56** gave the α, β-unsaturated ester **92** in 73% yield (2 steps) with 1:4 ratio, where the major is the desired *E* isomer. With diester **92** in hand, several deacetylation methods have been tried, but we failed to obtain alcohol *E*-**93**.



Scheme 2-22

The desired (*E*)-isomer was obtained as a major product from the Wittig reaction (Figure 2-9). However, all attempts to subject *E*-**92** to deprotection failed or resulted in decomposition. In some cases, the undesired cyclized product was obtained.

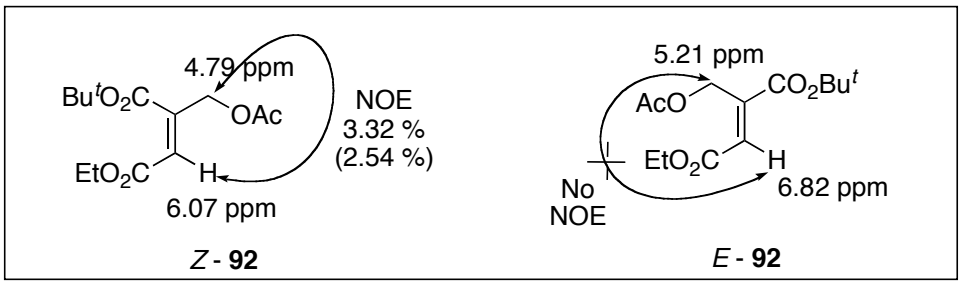
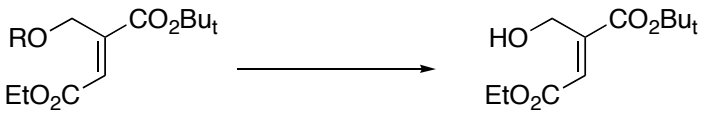


Figure 2-9

Other alternative routes were employed. Return to alcohol **90** as starting material, protection with several different protecting moieties has been tried. It was hope that other deprotection method would give the alcohol-ester *E*-**93**, which will then oxidize to aldehyde-ester **94**. However, the deprotection failed and only the cyclized product was obtained from the reaction mixture (Table 2-10).

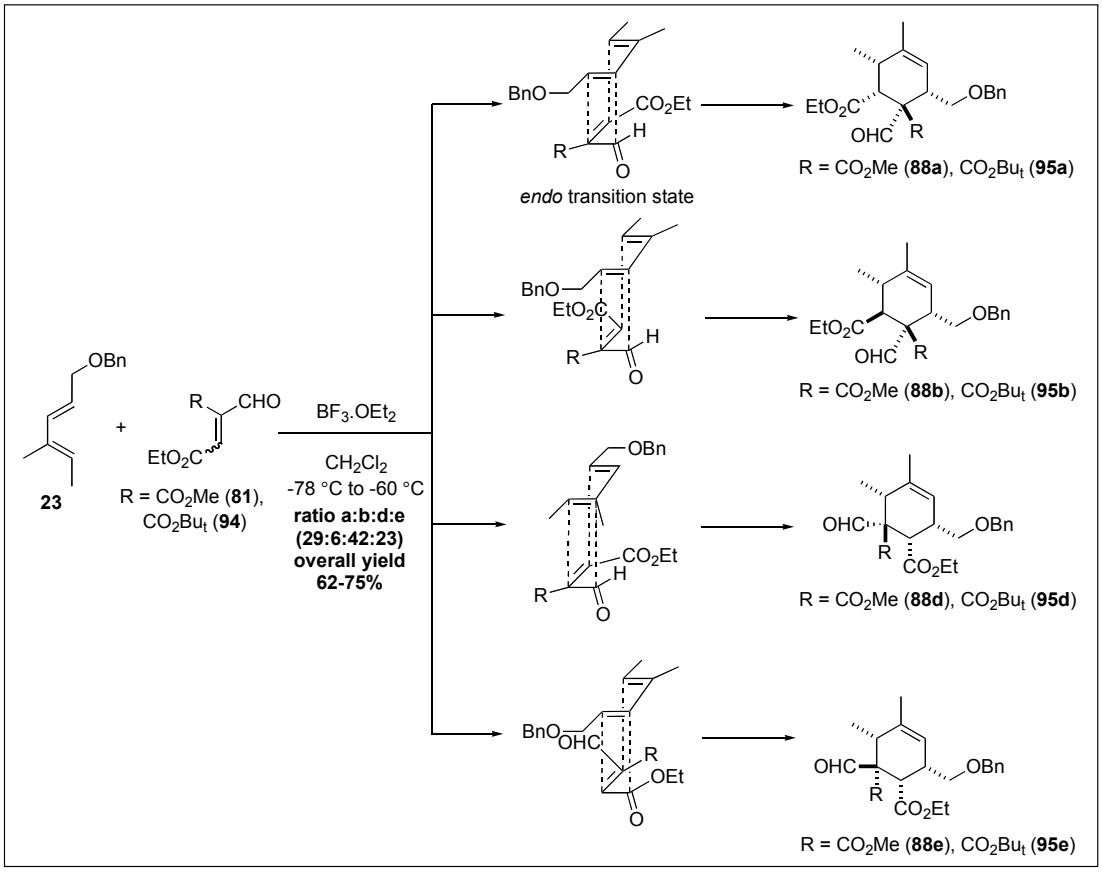
Table 2-10



E - **92** *E* - **93**

Entry	R	Conditions	Results
1	Ac	K_2CO_3 / MeOH	Transesterification occured, cyclized product
2	Ac	KCN / EtOH	No desired product
3	TMS	-	TMS cleavage during ozonolysis
4	TBDMS	TBAF / THF	Some cyclized product, decomposition
5	TBDMS	HF.Pyr / THF	Cyclized product

The regiochemistry and relative stereochemistry of the cycloadducts **79a**, **88a**, **95a**, **95b**, **95d**, and **95e** were elucidated by ^{1}H NMR, ^{13}C (DEPT), COSY, NOESY, HMQC and HMBC as depicted in Figure 2-10. The stereochemistry of the products suggests that due to secondary orbital interaction, the Diels-Alder reaction had proceeded by an *endo* transition state (Scheme 2-23) giving the different cycloadducts.



Scheme 2-23

Due to the bulkiness of either CO_2Me/CHO or CO_2Bu_t/CHO groups, the desired cycloadduct **A** was only obtained as minor product compared to cycloadduct **D** and **E**. The formation of cycloadduct **D** and **E** suggested that the CH_2OBn group and the 3-methyl group have a greater directive effect than the 4-methyl group on diene **23**. This also shows that the CO_2Et group also partakes in the cycloaddition reaction even in the presence of the reactive CHO group. Furthermore, only trace amount of cycloadduct **B** was obtained from the reaction mixture. This is due to the steric effect of the *endo* ester group which prevents the cycloaddition (Scheme 2-23, Figure 2-10).

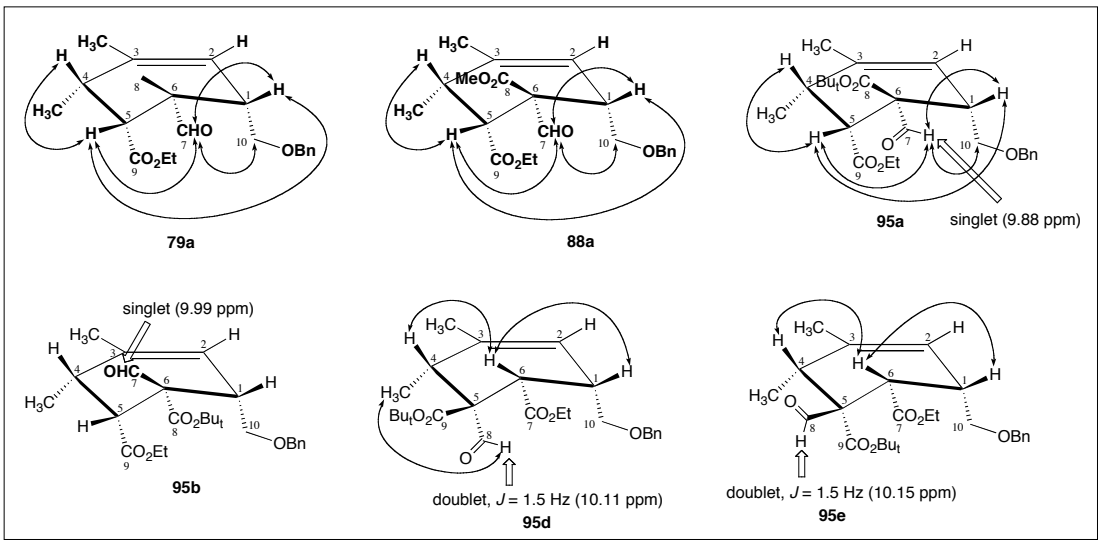


Figure 2-10

The relative stereochemistries of cycloadducts **79a**, **88a** and **95(a-e)** were confirmed by 2D NOESY and are consistent with the proposed structure. Cycloadduct **A** shows a high degree of interaction between the aldehydic proton and that of the neighbouring protons H-5 and H-1 attached to the newly formed ring system. The anomalous NOE effect of H-5 and H-1 can explained by the boat conformation adopted due to restriction about the alkene bond, effectively causing the molecule to adopt a bent axis about the C_3-CH_3 or CO_2Me/CHO and CO_2Bu_t/CHO groups, so that interaction is now possible but with reduced observed NOE interaction. Strong NOE correlation between H-6 to H-1 and H-6 to H-4 confirm the stereochemistries of cycloadduct **D** and **E**.

2.6 Conclusion

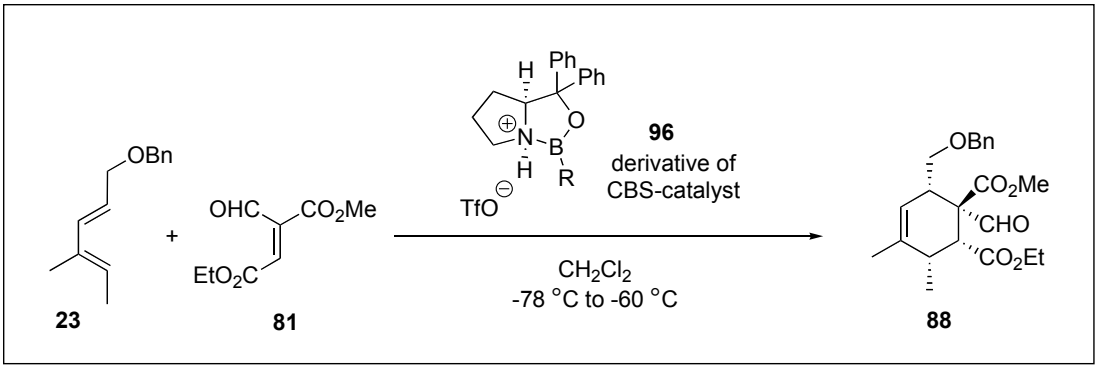
In conclusion, we have successfully developed a new methodology which may be applied to the synthesis of cytochalasans using Lewis acid catalyzed intermolecular Diels-Alder reaction as the key step. We manage to build the desired six-membered cyclohexane ring with correct stereochemistry that is the core ring skeleton found in the cytochalasans class of natural products.

2.7 Future works

Since cycloadduct **88a** only obtained as a minor product, effort to optimized the conditions and yields need to be done. Future work in this area would be to achieve the synthesis of (*E*)-dienophile **94** which is the desired dienophile for the cycloaddition to occur. With this, hopefully the yield can be optimized.

Having achieved a synthesis of cycloadduct **88a**, the next target in our synthetic exploration focuses on the development of strategies for the introduction of the lactam ring contain either indole, phenyl or isopropyl which will allow us to synthesize almost all the known cytochalasans.

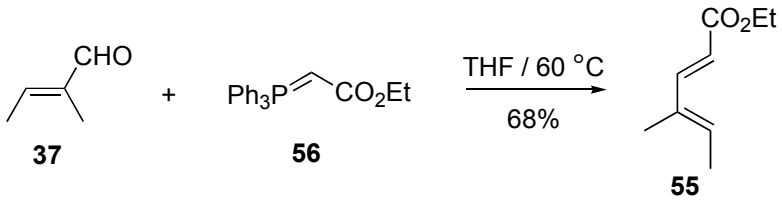
The exploration of an enantioselective synthesis route is also needed. This entails the stereoselective synthesis of cycloadduct **88a**. The enantioselective version of Diels-Alder reaction can be explored by the usage of a chiral ligand such as derivatives of CBS-catalyst (Corey-Bakshi-Shibata-catalyst, **96**) in the form of oxazoborolidinium cations (scheme 2-24).


OBn
OHC
CO2Me
EtO2C
23
81
H
Ph
Ph
O
N
B
H
R
TfO
96
derivative of
CBS-catalyst
CH2Cl2
-78 °C to -60 °C
OBn
CO2Me
CHO
CO2Et
88

Scheme 2-24

2.8 Experimental

(2*E*,4*E*)-Ethyl-4-methyl-2,4-hexadienoate (55)



Tiglic aldehyde **37** (10 g, 0.12 mol, 11.5 mL) was added to a solution of carb(ethoxymethylene) triphenyl phosphorane **56** (60 g, 0.18 mol) in THF (250 mL) at 60 °C. The reaction was stirred overnight at 60 °C. The reaction mixture was filtered. The filtrate was concentrated *in vacuo*. Purification *via* column chromatography afforded 68% (11.3 g) product **55**.

R_f = 0.77 (Hexane:EtOAc, 1:1);

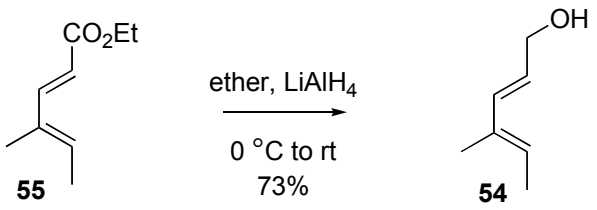
^{1}H NMR (300 MHz, $CDCl_3$): δ 1.26 (3H, t, *J* = 6.87 Hz, -$OCH_2C\mathbf{H}_3$), 1.74 (3H, s, $H_3CHC{=}CC\mathbf{H}_3$), 1.78 (3H, d, *J* = 7.05 Hz, $\mathbf{H}_3CHC{=}CCH_3$), 4.17 (2H, q, *J* = 6.87 Hz, -$OC\mathbf{H}_2CH_3$), 5.75 (1H, d, *J* = 15.4 Hz, HC=C**H**CO_2Et), 5.95 (1H, q, *J* = 7.05 Hz, $H_3C\mathbf{H}C{=}CCH_3$), 7.28 (1H, d, *J* = 15.4 Hz, **H**C=$CHCO_2$Et) ppm;

^{13}C NMR (75 MHz, $CDCl_3$): δ 11.7 (**C**H_3), 14.3 (-**C**H_3), 14.4 (-**C**H_3), 60.0 (-O**C**H_2-), 115.2 (-**C**H=CH-), 133.7 (-**C**H=C-), 136.2 (-**C**=CH-), 149.4 (-**C**H=CH-), 167.6 (-**C**=O) ppm;

FTIR (neat, cm^{-1}): 2985, 2940, 2870, 1704, 1621, 1446;

HRMS (EI $[M]^+$): *m/e* calculated for $[C_9H_{14}O_2]^+$ = 154.0994, found = 154.0996.

(2*E*,4*E*)-Ethyl-4-methyl-2,4-hexadien-1-ol (54)



55 (16.8 g, 0.12 mol) in dry ether (15 mL) was added dropwise to a suspension of lithium aluminium hydride at 0 °C under nitrogen. The reaction mixture was warmed slowly to room temperature and stirred for 4h. The mixture was quenched by adding saturated Na_2SO_4 solution dropwise at 0 °C. The mixture was filtered and the residue washed with ethyl acetate. The organic layer was dried over anhydrous $MgSO_4$ and rotary evaporated to give 73% (9.81 g) product **54**.

$\mathbf{R_f}$ = 0.52 (Hexane:EtOAc, 1:1);

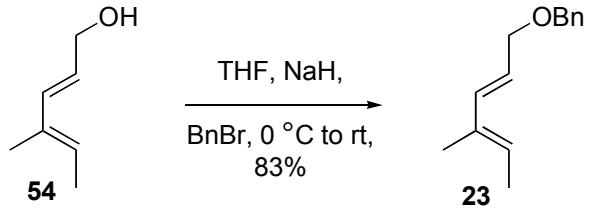
^{1}H NMR (300 MHz, $CDCl_3$): δ 1.60 (3H, s, $H_3CHC{=}CC\mathbf{H}_3$), 1.72 (3H, d, *J* = 6.77 Hz, $\mathbf{H}_3CHC{=}CCH_3$), 4.17 (2H, d, *J* = 6.18 Hz, -C$\mathbf{H}_2$OH), 5.56 (1H, q, *J* = 6.77 Hz, $CH_3\mathbf{H}C{=}CCH_3$), 5.69 (1H, dt, *J* = 15.6, 6.18 Hz, -CH=C**H**CH_2OH), 6.24 (1H, d, *J* = 15.6 Hz, -C**H**=$CHCH_2$OH) ppm;

^{13}C NMR (75 MHz, $CDCl_3$): δ 11.9 (-**C**H_3), 13.7 (-**C**H_3), 63.8 (-**C**H_2OH), 124.6 (-**C**H=C-), 127.4 (-**C**H=CH-), 133.7 (-CH=**C**H-), 136.2 (-CH=**C**-) ppm;

FTIR (neat, cm^{-1}): 3401, 2988, 2926, 2866, 1671, 1452;

HRMS (EI [M]$^+$): *m/e* calculated for $[C_7H_{12}O]^+$ = 112.0888, found = 112.0896.

(2*E*,4*E*)-1-(Benzyloxy)-4-methyl-2,4-hexadien-1-ol (23)



54 (4.00 g, 36 mmol) was added to a solution of sodium hydride (8.72 g, 0.36 mol) in THF (100 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 30 minutes after which benzyl bromide (6.82 g, 39 mmol, 4.8 mL) was added. The reaction was warmed slowly to room temperature and stirred for 3h. Saturated NH_4Cl solution was added drop-wise at 0 °C to quench the reaction. The reaction mixture was filtered, and washed with ethyl acetate. The combined organic layer was washed with water (1 x 100 mL), brine (1 x 100 mL), dried over anhydrous $MgSO_4$. The solvent was removed *in vacuo*. Purification *via* flash column chromatography yielded 83% (6.05 g) of product **23**.

$\mathbf{R_f}$ = 0.84 (Hexane:EtOAc, 2:1);

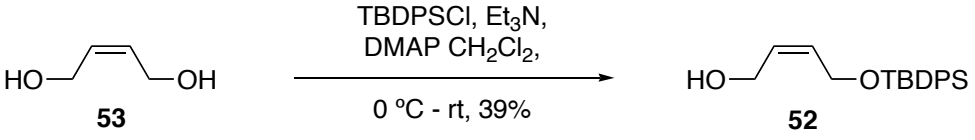
^{1}H NMR (300 MHz, $CDCl_3$): δ 1.25 (3H, s, $H_3CHC{=}CC\mathbf{H}_3$), 1.76 (3H, d, *J* = 6.81 Hz, $\mathbf{H}_3CHC{=}CCH_3$), 4.10 (2H, d, *J* = 6.35 Hz, -$C\mathbf{H}_2$OBn), 4.54 (2H, s, $OC\mathbf{H}_2C_6H_5$), 5.59 (1H, q, *J* = 6.81 Hz, $H_3C\mathbf{H}C{=}CCH_3$), 5.69 (1H, dt, *J* = 15.76, 6.35 Hz, $HC{=}C\mathbf{H}CH_2$OBn), 6.29 (1H, d, *J* = 15.76 Hz, $\mathbf{H}C{=}CHCH_2$OBn), 7.30 – 7.39 (5H, m, -$OCH_2C_6\mathbf{H}_5$) ppm;

^{13}C NMR (75 MHz, $CDCl_3$): δ 11.9 (-$\mathbf{C}H_3$), 13.7 (-$\mathbf{C}H_3$), 71.0 (-$O\mathbf{C}H_2$-), 71.8 (-$O\mathbf{C}H_2$-), 122.1 (-**C**H-), 127.3 (-**C**H-), 127.4 (-**C**H-), 127.5 (-**C**H-), 127.7 (-**C**H-), 128.2 (-**C**H-), 133.8 (-**C**-), 137.9 (-**C**-) ppm;

FTIR (neat, cm^{-1}): 3040, 2997, 2920, 2853, 1709, 1452;

HRMS (EI [M]$^+$): *m/e* calculated for $[C_{14}H_{18}O]^+$ = 202.1358, found = 202.1353.

(2*Z*)-1-(*tert*-Butyldiphenylsilyloxy)-1,4-butendiol (52)



Triethylamine (11.1 g, 0.11 mol, 16 mL) was added to a solution of dimethyl aluminium hydride (1.4 g, 0.01 mol) in CH_2Cl_2 (150 mL). But-2-ene-1,4 diol **53** (10.0 g, 0.11 mol, 9.5 mL) was added to the reaction mixture followed by *t*-butyldiphenylsilylchloride (31.2 g, 0.11 mol, 30 mL) at 0 °C. The mixture was stirred overnight. The reaction was quenched by adding ice water. The aqueous layer was extracted with CH_2Cl_2 (3 x 100 mL). The combined organic layer was washed with water (1 x 50 mL), brine (1x 50 mL) and dried over anhydrous $MgSO_4$. The solvent was removed *in vacuo*. Purification *via* column chromatography eluted the pure product **52** in 39% (14.1 g) yield.

R_f = 0.45 (Hexane:EtOAc, 2:1);

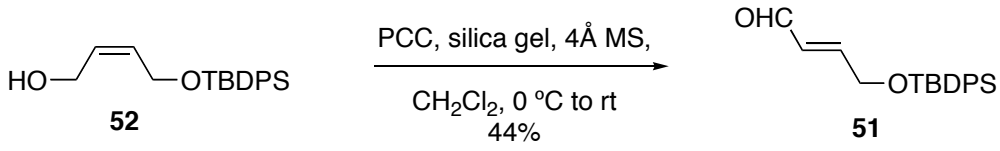
^{1}H NMR (300 MHz, $CDCl_3$): δ 1.08 (9H, s, $OSi(C_6H_5)_2C(CH_3)_3$), 1.91 (1H, brs, O**H**), 4.02 (2H, d, *J* = 5.70 Hz, C**H**$_2$OH), 4.29 (2H, d, *J* = 4.62 Hz, C**H**$_2$OTBDPS), 5.60 -5.69 (1H, m, C**H**CH_2OH), 5.71 – 5.77 (1H, m, C**H**CH_2OTBDPS), 7.40 – 7.76 (10H, m, $OSi(C_6H_5)_2C(CH_3)_3$) ppm;

^{13}C NMR (75 MHz, $CDCl_3$): δ 19.0 (-**C**$(CH_3)_3$), 26.7 (-C(**C**$H_3)_3$), 58.5 (-O**C**H_2-), 60.1 (-O**C**H_2-), 127.6 (-**C**H-), 129.7 (-**C**H-), 129.8 (-**C**H-), 130.7 (-**C**H-), 133.3 (-**C**H-), 135.5 (-**C**-) ppm;

FTIR (neat, cm^{-1}): 3447, 3019, 2928, 2861, 1428;

HRMS (EI [M-C_4H_9]$^+$): *m/e* calculated for $[C_{16}H_{17}O_2Si]^+$ = 269.0998, found = 269.0998.

(2*E*)-4-(*tert*-Butyldiphenylsilyloxy)-2-butenal (51)



52 (9.07 g, 28 mmol) in CH_2Cl_2 (30 mL) was added to pyridinium chlorochromate (56 g, 56 mmol), 4Å molecular sieve (9 g) and silica gel (9 g) in CH_2Cl_2 (150 mL) at 0 °C. The reaction mixture was warmed slowly to room temperature and stirred for 4h. The reaction mixture was filtered through a sintered glass funnel packed with silica gel and washed with CH_2Cl_2. The filtrate was dried over $MgSO_4$ and rotary evaporated. Purification through column chromatography yielded 34% (3.1 g) product **51**.

$\mathbf{R_f}$ = 0.63 (Hexane:EtOAc, 2:1);

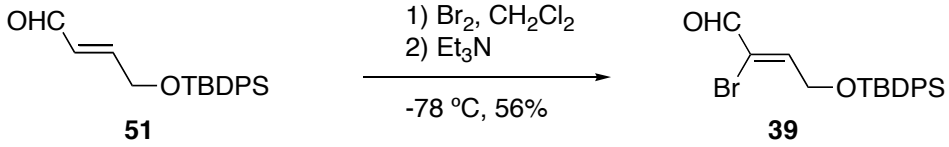
^{1}H NMR (300 MHz, $CDCl_3$): δ 1.08 (9H, s, -C(C**H**$_3$)$_3$), 4.45 (2H, d, *J* = 2.37, -C**H**$_2$OTBDPS), 6.57 (1H, dd, *J* = 15.5, 8.10 Hz, -C**H**CHO), 6.84 (1H, dt, *J* = 15.5, 2.37 Hz, -C**H**CH$_2$OTBDPS), 7.40-7.67 (10H, m, -Ph-**H**), 9.60 (1H, d, *J* = 8.10 Hz, -C**H**O) ppm;

^{13}C NMR (75 MHz, $CDCl_3$): δ 19.1 (-**C**(CH$_3$)$_3$), 26.6 (-C(**C**H$_3$)$_3$), 62.8 (-O**C**H$_2$-), 127.7 (-**C**H-), 129.8 (-**C**H-), 130.6 (-**C**H-), 132.6 (-**C**H-), 135.3 (-**C**-), 155.8 (-**C**H-), 193.0 (-**C**=O) ppm;

FTIR (neat, cm^{-1}): 3073, 2965, 2939, 2860, 1658, 1472;

HRMS (EI [M]$^+$): *m/e* calculated for $[C_{20}H_{24}O_2Si]^+$ = 324.1546 found = 324.1546.

(*Z*)-2-bromo-4-(*tert*-butyldiphenylsilyloxy)but-2-enal (39)



51 **39**

To a solution of **51** (0.60 g, 1.8 mmol) in CH_2Cl_2 (20 mL) was treated with Br_2 (0.29 g, 1.8 mmol) at -78 ºC. The resulting colourless solution was treated with additional Br_2 until reddish brown colour persisted. The reaction mixture was warmed to 0 ºC and stirred for 20 minutes. The mixture was then cooled to -78 ºC and Et_3N (0.18 g,

1.8 mmol) was added dropwise with vigorous stirring. After completed, the reaction mixture was filtered through sintered glass funnel and the residue was washed with copious amount of dry ether. The filtrate was washed with saturated $Na_2S_2O_3$ solution, brine, dried over anhydrous $MgSO_4$ and concentrated. The residue was chromatographed (hexane:ether = 99:1) affording 1.38 g of **39** as a colourless oil (56%).

$\mathbf{R_f}$ = 0.50 (Hexane:Ether, 6:1);

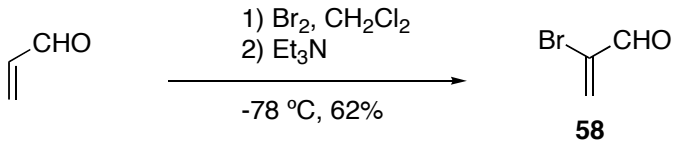
^{1}H NMR (300 MHz, $CDCl_3$): δ 1.10 (9H, s, -C(C**H**$_3$)$_3$), 4.62 (2H, d, *J* = 4.79 Hz, -C**H**$_2$-OTBDPS), 7.31 (1H, t, *J* = 4.79 Hz, -C=C**H**-), 7.39-7.69 (10H, m, -Ph-**H**), 9.15 (s, 1H -C**H**O) ppm;

^{13}C NMR (75 MHz, $CDCl_3$): δ 19.1 (-**C**(CH$_3$)$_3$), 26.6 (-C(**C**H$_3$)$_3$), 63.9 (-O**C**H$_2$-), 122.0 (-**C**H-), 127.8 (-**C**H-), 130.0 (-**C**-), 132.6 (-**C**H-), 135.4 (-**C**-), 154.5 (-**C**H-), 185.0 (-**C**=O) ppm;

FTIR (neat, cm^{-1}): 3057, 2963, 2930, 2858, 1709, 1622, 1428;

HRMS (EI [M-C_4H_9]$^+$): *m/e* calculated for $[C_{16}H_{14}O_2Si^{79}Br]^+$ = 344.9946 found = 344.9956.

Bromoacrolein (58)



58

A flame-dried 250 mL three-necked flask equipped with a mechanical stirrer and an addition funnel was charged with a solution of acrolein (33.5 mL, 0.5 mol) in dichloromethane (20 mL). The mixture was cooled to -78 ºC and bromine (25.8 mL, 0.5 mol) was added dropwise through the addition funnel. The resulting colorless solution was treated with additional bromine, dropwise, until a reddish brown color

persisted. Acrolein was then added dropwise through the addition funnel until the reddish brown color disappeared. The solution was stirred at 0 ºC for 20 min. The solution was cooled to -78 ºC and triethylamine (70.0 mL, 1.0 mol) was added slowly with vigorous mechanical stirring. Dropwise addition of triethylamine and efficient cooling are essential to prevent decomposition of product during the highly exothermic reaction. Copious salt precipitation was observed and the solid suspension was treated with 200 mL ether. The suspension was rapidly filtered, and the solids were repeatedly washed with 300 mL ether. The filtrate was washed once with 50 mL saturated sodium thiosulfate and twice with brine. The organic layer was dried thoroughly with $MgSO_4$, filtered and solvent removed on a rotary evaporator with the bath temperature kept at 0 ºC. Distillation of the crude product at 10-20 mmHg using an oil bath maintained at 90 ºC and a receiver temperature at -78 ºC yielded 34 g (62%) product **58** as a pale yellow oil.

R_f = 0.57 (Hexane:EtOAc, 2:1);

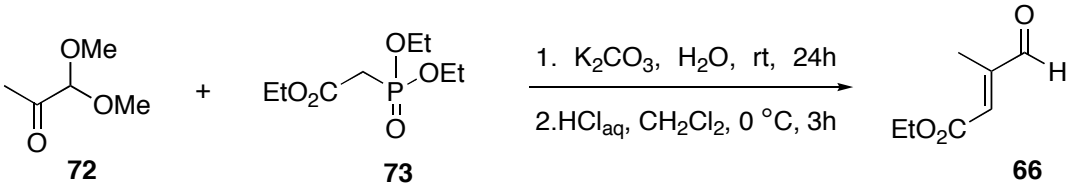
^{1}H NMR (300 MHz, $CDCl_3$): δ 6.89 (2H, s, -C=C**H**$_2$), 9.23 (1H, s, -C**H**O) ppm;

^{13}C NMR (75 MHz, $CDCl_3$): δ 132.3 (-**C**=CH$_2$), 136.5 (-C=**C**H$_2$), 185.6 (-**C**=O) ppm;

FTIR (neat, cm^{-1}): 3070, 2989, 2835, 1698;

HRMS (EI [M]$^+$): *m/e* calculated for $[C_3H_3O^{79}Br]^+$ = 133.9367 found = 133.9367.

(*E*)-ethyl 3-methyl-4-oxobut-2-enoate (66)



A mixture of 1,1-dimethoxyacetone (**72**) (5.91 g, 50 mmol) and ethyl 2-

(diethoxyphosphoryl)acetate (**73**) (13.45 g, 60 mmol) was added dropwise to a suspension of K_2CO_3 (17.28 g) in 10 mL of water at room temperature. After the addition was complete, stirring was continued at room temperature for an additional 24h. The insoluble matter was then removed by filtration and washed with ether. The organic phase was separated and washed with brine to neutrality. After drying and evaporation of solvent, the product was purified by distillation under vacuum, which yields a mixture of *E* and *Z* acetal esters as a colorless oil.

HCl (3 N, 15 mL) was added dropwise to a solution of the above obtained *E* and *Z* acetal esters in 15 mL CH_2Cl_2 at 0 °C. The resulting mixture was stirred for another 2h at 0 °C. The organic layer was separated and washed with a saturated aqueous solution of $NaHCO_3$ and brine, and dried over anhydrous Na_2SO_4. Solvent was removed under vacuum. The crude product was purified by vacuum distillation to yield 7.1 g of the *E* isomer of **66** (yield: 85%).

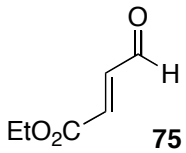
$\mathbf{R_f}$ = 0.45 (Hexane:EtOAc, 4:1);

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.34 (3H, t, *J* = 7.03 Hz, -$OCH_2C\mathbf{H}_3$), 2.16 (3H, d, *J* = 1.76 Hz, -$CC\mathbf{H}_3$), 4.28 (2H, q, *J* = 7.03 Hz, -$OC\mathbf{H}_2CH_3$), 6.50 (1H, q, *J* = 1.76 Hz, -C**H**=C-), 9.55 (1H, s, C**H**O) ppm;

(*E*)-ethyl 4-oxobut-2-enoate (75) and (*Z*)-ethyl 3-bromo-4-oxobut-2-enoate (76)

Following the described procedure for the preparation of dienophile **66**; dienophile **75** was obtained in 78% (2 steps) and dienophile **76** was obtained in 30% yield.

(*E*)-ethyl 4-oxobut-2-enoate (75)

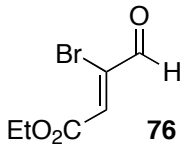


75

$\mathbf{R}_f$ = 0.43 (Hexane:EtOAc, 4:1);

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.34 (3H, t, *J* = 6.96 Hz, -$OCH_2C\mathbf{H}_3$), 4.30 (2H, q, *J* = 6.96 Hz, -$OC\mathbf{H}_2CH_3$), 6.72 (1H, q, *J* = 16.02 Hz, -C**H**=CH-), 6.97 (1H, dd, *J* = 7.65, 16.02 Hz, -CH=C**H**-), 9.76 (1H, dd, *J* = 7.65, 0.69 Hz, -C**H**O) ppm

(*Z*)-ethyl 3-bromo-4-oxobut-2-enoate (76)



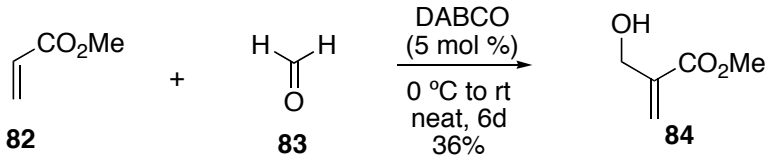
76

$\mathbf{R}_f$ = 0.62 (Hexane:EtOAc, 4:1);

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.36 (3H, t, *J* = 7.32 Hz, -$OCH_2C\mathbf{H}_3$), 4.34 (2H, q, *J* = 7.32 Hz, -$OC\mathbf{H}_2CH_3$), 7.28 (1H, s, -C=C**H**-), 9.26 (1H, s, -C**H**O) ppm;

^{13}C NMR (75 MHz, $CDCl_3$): δ 13.9 (-$OCH_2\mathbf{C}H_3$), 61.8 (-$O\mathbf{C}H_2CH_3$), 133.9 (-**C**=CH-), 136.0 (-C=**C**H-), 163.1 (-**C**O_2Et), 185.9 (-**C**HO) ppm;

methyl 2-(hydroxymethyl)acrylate (84)



82 **83** **84**

Methyl acrylate (**82**) (1 mol, 86.1 g), DABCO (0.1 mol, 11.2 g) and formaldehyde (**83**) (1.5 mol, 41,7 mL) were stirred at room temperature for six days. The product was extracted with ethyl acetate (x3). The organic extracts were washed with brine,

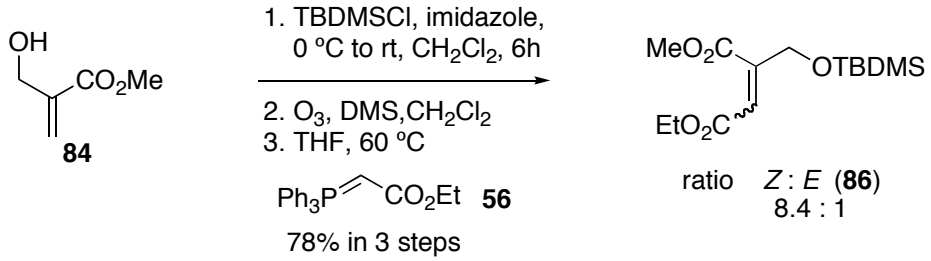
dried with anhydrous $MgSO_4$, concentrated in *vacuo* and purified by distillation, affording 41.8 g of pure **84** as colourless oil (36% yield). Bp: 105 ºC / 4.5 mmHg.

$\mathbf{R_f}$ = 0.25 (Hexane:EtOAc, 2:1);

^{1}H NMR (300 MHz, $CDCl_3$): δ 3.75 (3H, s, -C**H**$_3$), 4.30 (2H, d, *J* = 5.57 Hz, -C**H**$_2$OH), 5.82 (1H, d, *J* = 1.21 Hz, -C=C**H**$_2$-), 6.22 (1H, s, -C=C**H**$_2$-) ppm;

^{13}C NMR (75 MHz, $CDCl_3$): δ 51.8 (-O**C**H$_3$), 62.2 (-**C**H$_2$OH), 125.6 (-C=**C**H$_2$), 139.4 (-**C**=CH$_2$), 166.7 (-**C**=O) ppm

4-ethyl 1-methyl 2-((*tert*-butyldimethylsilyloxy)methyl)but-2-enedioate (86)



To a solution of **84** (5 g, 43 mmol) in CH_2Cl_2 (100 mL) was added imidazole (5.85 g, 86 mmol) at 0 °C. After imidazole was dissolved, TBDMSCl (7.13 g, 47.3 mmol) was added to the reaction mixture. The mixture was at 0 ºC to room temperature for 6h. The reaction was poured into ice water and extracted with ethyl acetate (x3). The combined organic layer was washed with brine and dried over anhydrous $MgSO_4$. The solvent was removed in *vacuo*. The crude product was then used for ozonolysis at -78 ºC in CH_2Cl_2 as the solvent. The reaction was quenched by adding DMS (3 equiv) and let it stirred for overnight at room temperature. After washed with water, dried over $MgSO_4$ and concentrated, the crude product was further subjected for Wittig reaction with **56** (22.47 g, 64.5 mmol) in THF at 60 ºC for 12h. The solvent was removed and purification *via* column chromatography eluted the pure product **86** in 78% (10.15 g) yield in 3 steps. (*Z:E* = 8.4:1)

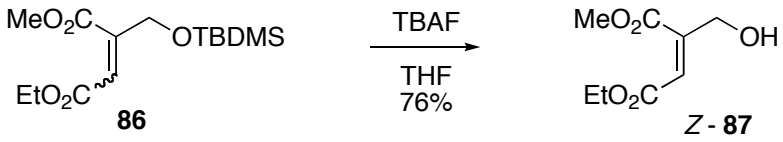
***Z* isomer:**

$\mathbf{R}_f$ = 0.73 (Hexane:EtOAc, 4:1);

^{1}H NMR (500 MHz, $CDCl_3$): δ 0.07 (6H, s, -Si-(CH_3)$_2$), 0.89 (9H, s, -C(CH_3)$_3$), 1.27 (3H, t, *J* = 7.1 Hz, -OCH_2CH_3), 3.78 (3H, s, -CO_2**Me**), 4.18 (2H, t, *J* = 7.1 Hz, -OCH_2CH_3), 4.36 (2H, d, *J* = 2.05 Hz, -CH_2OTBDMS), 6.15 (1H, t, *J* = 2.05 Hz, -C=C**H**-) ppm;

^{13}C NMR (75 MHz, $CDCl_3$): δ -5.6 (-Si(CH_3)$_2$), 14.1 (-CH_3), 18.2 (-**C**(CH_3)$_3$), 25.7 (-C(CH_3)$_3$), 52.2 (-O**Me**), 60.9 (-OCH_2-), 62.5 (-OCH_2-), 120.1 (-**C**H=C-), 147.1 (-CH=**C**-), 165.5 (-**C**=O), 167.2 (-**C**=O) ppm;

4-ethyl 1-methyl 2-(hydroxymethyl)maleate (87)



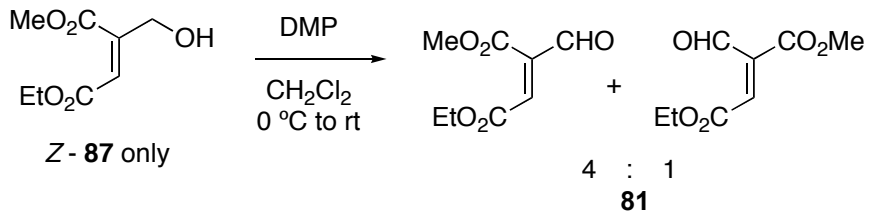
To a solution of **86** (0.91 g, 3 mmol) in THF (9 mL) was treated with TBAF (4.5 mL, 1.0 M in THF solution, 4.5 mmol) at room temperature. The mixture was stirred for 30 minutes. After the reaction was completed (monitor by TLC), THF was removed in *vacuo*. The residue was purified by flash chromatography on silica gel to afford alcohol **87** as a colorless oil, 0.43 g (76%).

$\mathbf{R}_f$ = 0.15 (Hexane:EtOAc, 4:1);

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.29 (3H, t, *J* = 7.1 Hz, -OCH_2CH_3), 3.82 (3H, s, -CO_2**Me**), 4.21 (2H, q, *J* = 7.1 Hz, -OCH_2CH_3), 4.39 (2H, d, *J* = 1.6 Hz, -CH_2OH), 6.20 (1H, t, *J* = 1.6 Hz, -C=C**H**-) ppm;

2.3% NOE

4-ethyl 1-methyl 2-formylmaleate (81)



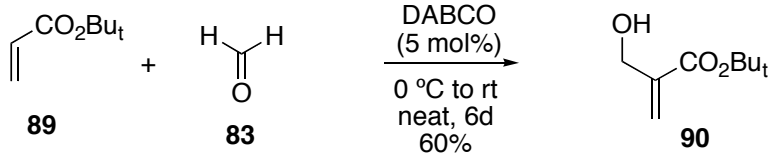
To a solution of Dess-Martin reagent (0.64 g, 1.5 mmol) in anhydrous CH_2Cl_2 (3 mL) was added dropwise of **87** (0.19 g, 1 mmol) prediluted in CH_2Cl_2 (1 mL) at 0 °C. The reaction mixture was stirred under nitrogen at 0 °C for 30 minutes. After completion, the reaction mixture was filtered through selite and rinse with ether. The combine etherate layer was washed with brine, dried over anhydrous $MgSO_4$ and concentrated in *vacuo* to give **81** as a colorless oil (**81** was sensitive to purification, NMR determination was done from the crude product ^{1}H NMR).

$\mathbf{R}_f$ = 0.43 (Hexane:EtOAc, 4:1);

major ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.32 (3H, t, *J* = 7.1 Hz, -$OCH_2C\mathbf{H}_3$), 3.88 (3H, s, -$CO_2\mathbf{Me}$), 4.28 (2H, q, *J* = 7.1 Hz, -$OC\mathbf{H}_2CH_3$), 6.74 (1H, s, -C=C**H**-), 9.65 (1H, s, -C**H**O) ppm

minor ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.32 (3H, t, *J* = 7.1 Hz, -$OCH_2C\mathbf{H}_3$), 3.86 (3H, s, -$CO_2\mathbf{Me}$), 4.28 (2H, q, *J* = 7.1 Hz, -$OC\mathbf{H}_2CH_3$), 7.09 (1H, s, -C=C**H**-), 10.17 (1H, s, -C**H**O) ppm

***tert*-butyl 2-(hydroxymethyl)acrylate (90)**



Tert-butyl acrylate (10 mL, 68.9 mmol), DABCO (7.7 g, 68.9 mmol) and formaldehyde (0.689 mol, 100 mL) were stirred at room temperature for six days. The

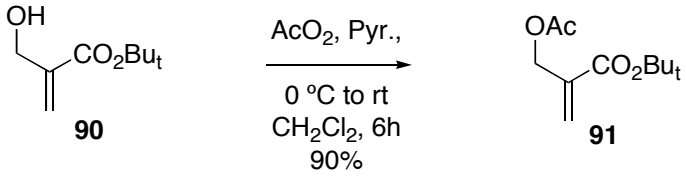
product was extracted with ether (x5). The organic extracts was washed with brine, dried with anhydrous $MgSO_4$, concentrated in *vacuo* and purified by column chromatography, affording 6.54 g of pure **90** as colourless oil (60% yield).

$\mathbf{R}_f$ = 0.41 (Hexane:EtOAc, 4:1);

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.51 (9H, s, -C(C**H**$_3$)$_3$), 4.28 (2H, d, *J* = 6.83 Hz, -C**H**$_2$OH), 5.74 (1H, d, *J* = 1.21 Hz, -C=C**H**$_2$-), 6.15 (1H, s, -C=C**H**$_2$-) ppm

^{13}C NMR (75 MHz, $CDCl_3$): δ 28.0 (-OC(**C**H$_3$)$_3$), 62.7 (-**C**H$_2$OH), 81.3 (-O**C**(CH$_3$)$_3$), 124.7 (-C=**C**H$_2$), 140.9 (-**C**=CH$_2$), 165.7 (-**C**=O) ppm

***tert*-butyl 2-(acetoxymethyl)acrylate (91)**



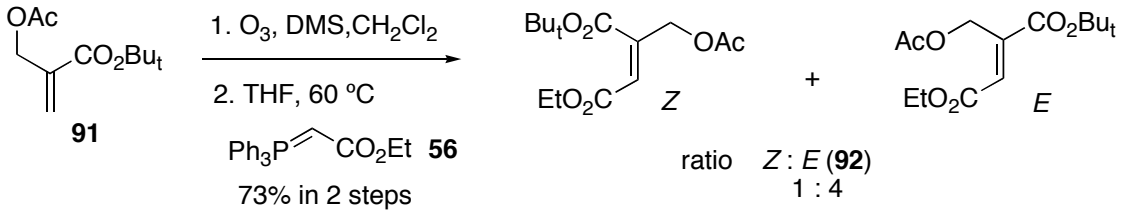
To a solution of **90** (6.4 g, 40.4 mmol) in CH_2Cl_2 (100 mL) was added pyridine (6.54 mL, 80.8 mmol) at 0 °C. After stirred for 10 minutes, acetic anhydride (7.7 mL, 80.8 mmol) was added to the reaction mixture. The mixture was at 0 ºC to room temperature for 6h. The reaction was poured into ice water and extracted with ether (x3). The combined organic layer was washed with copper sulfate solution, water, brine and dried over anhydrous $MgSO_4$. The solvent was removed in *vacuo*. Purification by column chromatography provided **91** in 90% yield (7.30 g).

$\mathbf{R}_f$ = 0.57 (Hexane:EtOAc, 4:1);

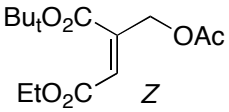
^{1}H NMR (300 MHz, $CDCl_3$): δ 1.46 (9H, s, -C(C**H**$_3$)$_3$), 2.06 (3H, s, O**Ac**), 4.73 (2H, s, -C**H**$_2$OAc), 5.69 (1H, s, -C=C**H**$_2$-), 6.21 (1H, s, -C=C**H**$_2$-) ppm

^{13}C NMR (75 MHz, $CDCl_3$): δ 20.7 (-O**Ac**), 27.9 (-OC(**C**H$_3$)$_3$), 62.5 (-O**C**H$_2$-), 81.2 (-O**C**(CH$_3$)$_3$), 125.9 (-C=**C**H$_2$), 136.8 (-**C**=CH$_2$), 164.2 (-**C**=O), 170.2 (-**C**=O) ppm

1-*tert*-butyl 4-ethyl 2-(acetoxymethyl)maleate (92)



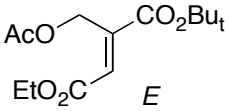
To a solution of **91** (5 g, 25 mmol) in CH_2Cl_2 was subjected for ozonolysis at -78 ºC. After completion (~30 minutes), the reaction was quenched by adding DMS (3 equiv) and let it stirred for overnight at room temperature. After washed with water, dried over $MgSO_4$ and concentrated, the crude product was further subjected for Wittig reaction with **56** (13 g, 37.5 mmol) in THF at 60 ºC for 12h. The solvent was removed and purification *via* column chromatography eluted the pure product **92** in 73% (10.15 g) yield in 2 steps. (*Z:E* = 1:4)



$\mathbf{R}_f$ = 0.59 (Hexane:EtOAc, 4:1);

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.30 (3H, t, *J* = 7.2 Hz, -$OCH_2C\mathbf{H}_3$), 1.53 (9H, s, -$C(C\mathbf{H}_3)_3$), 2.12 (3H, s, -O**Ac**), 4.23 (2H, q, *J* = 7.2 Hz, -$OC\mathbf{H}_2CH_3$), 4.79 (2H, d, *J* = 1.55 Hz, -$C\mathbf{H}_2OAc$), 6.07 (1H, t, *J* = 1.65 Hz, -C=C**H**-) ppm;

^{13}C NMR (125 MHz, $CDCl_3$): δ 14.1 (-$\mathbf{C}H_3$), 20.6 (-$\mathbf{C}H_3$), 27.9 (-$OC(\mathbf{C}H_3)_3$), 61.0 (-$O\mathbf{C}H_2$-), 63.1 (-$O\mathbf{C}H_2$-), 83.0 (-$O\mathbf{C}(CH_3)_3$), 122.5 (-**C**H=C-), 141.8 (-CH=**C**-), 164.4 (-**C**=O), 164.8 (-**C**=O), 169.9 (-**C**=O) ppm



$\mathbf{R}_f$ = 0.63 (Hexane:EtOAc, 4:1);

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.32 (3H, t, *J* = 7.1 Hz, -$OCH_2C\mathbf{H}_3$), 1.51 (9H, s, -$C(C\mathbf{H}_3)_3$), 2.06 (3H, s, -O**Ac**), 4.26 (2H, q, *J* = 7.1 Hz, -$OC\mathbf{H}_2CH_3$), 5.21 (2H, s, -$C\mathbf{H}_2OAc$), 6.82 (1H, s, -C=C**H**-) ppm

^{13}C NMR (125 MHz, $CDCl_3$): δ 14.1 (-$\mathbf{C}H_3$), 20.7 (-$\mathbf{C}H_3$), 28.0 (-$OC(\mathbf{C}H_3)_3$), 58.1 (-$O\mathbf{C}H_2$-), 61.2 (-$O\mathbf{C}H_2$-), 82.5 (-$O\mathbf{C}(CH_3)_3$), 130.0 (-**C**H=C-), 141.6 (-CH=**C**-), 164.3 (-**C**=O), 164.9 (-**C**=O), 170.2 (-**C**=O) ppm

Diels-Alder Reactions

General Procedure using $In(OTf)_3$ as Catalyst

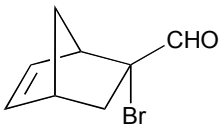
The dienophile (1 mmol) in CH_2Cl_2 (1 mL) was added dropwise to a stirred mixture of 4Å molecular sieve (100 mg, excess) and indium triflate (0.28 mg, 0.5 mmol) in CH_2Cl_2 (1 mL) at 0 °C. Subsequently, the diene (3 mmol) pre-diluted in CH_2Cl_2 (1 mL) was added dropwise. The whole reaction was maintained at 0 °C with constant stirring. The reaction was quenched with saturated $NaHCO_3$ (2 mL). The organic layer was extracted with CH_2Cl_2 (3 x 5 mL), washed with saturated $NaHCO_3$ (2 x 5 mL), and dried over anhydrous $MgSO_4$. The filtrate was filtered and concentrated. Purification by flash column chromatography afforded the pure compound.

General Procedure using $BF_3.OEt_2$ as Catalyst

The dienophile (1 mmol) in CH_2Cl_2 (1 mL) was added dropwise to a stirred solution of 4Å molecular sieve (100 mg, excess) and cooled to -78 °C for 15 minutes. Then boron trifluoride diethyrate (0.06 mL, 0.5 mmol) was added dropwise. Subsequently, the diene (3 mmol) pre-diluted in CH_2Cl_2 (1 mL) was added dropwise. The whole reaction was maintained at -78 °C with constant stirring for 16h. The reaction was quenched with saturated $NaHCO_3$ (2 mL). The organic layer was extracted with

CH_2Cl_2 (3 x 5 mL), washed with saturated $NaHCO_3$ (2 x 5 mL), and dried over anhydrous $MgSO_4$. The filtrate was filtered and concentrated. Purification by flash column chromatography afforded the pure compound.

2-bromo-bicyclo[2.2.1]hept-5-ene-2-carbaldehyde



Colorless oil (74%);

R_f = 0.65 (hexane/ethyl acetate, 4:1);

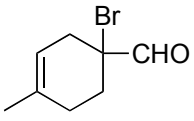
^{1}H NMR (300 MHz, $CDCl_3$): δ 1.32 (1H, d, *J* = 9.4 Hz, -C**H**$_2$-), 1.42-1.59 (2H, m, -C**H**$_2$-), 2.65 (1H, dd, *J* = 13.6, 3.5 Hz, -C**H**$_2$-), 2.97 (1H, brs, -C**H**-), 3.25 (1H, brs, -C**H**-), 6.14 (1H, dd, *J* = 5.6, 3.1 Hz, -HC=C**H**-), 6.45 (1H, dd, *J* = 5.6, 3.1 Hz, -**H**C=CH-), 9.54 (1H, s, *exo* C**H**O);

^{13}C NMR (75 MHz, $CDCl_3$): δ 36.9 (-**C**H$_2$-), 42.4 (-**C**H-), 46.7 (-**C**H-), 49.6 (-**C**H$_2$-), 72.6 (-**C**-CHO), 133.8 (-CH=**C**H-), 140.0 (-**C**H=CH-), 191.9 (-**C**HO);

FTIR (neat, cm^{-1}): 2978, 1722;

HRMS (EI [M^+]): *m/e* calculated for $[C_8H_{19}BrO]^+$ = 199.9837; Found = 199.9834

1-Bromo-4-methyl-cyclohex-3-enecarbaldehyde (59)



Colorless oil (64%);

R_f = 0.67 (hexane/ethyl acetate, 4:1);

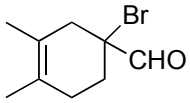
^{1}H NMR (300 MHz, $CDCl_3$): δ 1.67 (3H, brs, -C**H**$_3$), 2.28-2.09 (4H, m, -C**H**$_2$-C**H**$_2$-C-CHO), 2.62 (1H, bd, *J* = 18.0 Hz, -C**H**$_2$-C-CHO), 2.79 (1H, brd, *J* = 18.1 Hz, -C**H**$_2$-C-CHO), 5.33 (1H, brs, -C=C**H**-), 9.36 (1H, s, -C**H**O);

^{13}C NMR (75 MHz, $CDCl_3$): δ 23.1 (-**C**H$_3$), 28.5 (-**C**H$_2$-), 30.9 (-**C**H$_2$-), 34.4 (-**C**H$_2$-), 67.0 (-**C**-CHO), 117.0 (-C=**C**H-), 134.0 (-**C**=CH-), 192.2 (-**C**=O);

FTIR (neat, cm^{-1}): 2916, 1726, 1638;

HRMS (ESI [M-Br]): m/e calculated for $C_8H_{11}O$ = 123.0810, found = 123.0810

1-bromo-3,4-dimethyl-cyclohex-3-enecarbaldehyde



Colorless oil (68%);

R$_f$ = 0.67 (hexane/ethyl acetate, 4:1);

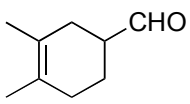
^{1}H NMR (300 MHz, $CDCl_3$): δ 1.62 (3H, s, -C**H**$_3$), 1.65 (3H, s, -C**H**$_3$), 2.27-2.08 (4H, m, -C**H**$_2$-C**H**$_2$-C-CHO), 2.56 (1H, brd, *J* = 17.8 Hz, -C**H**$_2$CHO), 2.74 (1H, brd, *J* = 17.4 Hz, -C**H**$_2$CHO), 9.34 (1H, s, -C**H**O);

^{13}C NMR (75 MHz, $CDCl_3$): δ 18.6 (-**C**H$_3$), 19.0 (-**C**H$_3$), 29.9 (-**C**H$_2$-), 31.2 (-**C**H$_2$-), 40.0 (-**C**H$_2$-), 67.7 (-**C**-CHO), 122.2 (-C=**C**-), 125.4 (-**C**=C-), 192.2 (-**C**=O);

FTIR (neat, cm^{-1}): 2916, 1726, 1641;

HRMS (ESI [M^+]): calculated for $C_9H_{13}BrO$ = 216.0150; found = 216.0141.

3,4-dimethylcyclohex-3-enecarbaldehyde



Colorless oil (60%);

R$_f$ = 0.64 (hexane/ethyl acetate, 4:1);

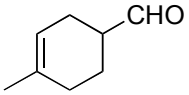
^{1}H NMR (300 MHz, $CDCl_3$): δ 1.61 (3H, s, -C=C-C**H**$_3$), 1.65 (3H, s, -C=C-C**H**$_3$), 1.94 - 2.51 (7H, m, -C**H**$_2$C-CHO, -C**H**-CHO, -C**H**$_2$-C**H**$_2$-C-CH$_3$), 9.67 (1H, d, *J* = 1.41 Hz, -C**H**O);

^{13}C NMR (75 MHz, $CDCl_3$): δ 18.9 (-**C**H$_3$), 19.0 (-**C**H$_3$), 22.8 (-**C**H$_2$-), 30.1 (-**C**H$_2$-), 30.5 (-**C**H$_2$-), 46.9 (-**C**H-CHO), 123.4 (-C=**C**-), 125.8 (-**C**=C-), 204.7 (-**C**=O);

FTIR (neat, cm^{-1}): 2916, 1725, 1641;

HRMS (ESI [M$^+$]): calculated for $C_9H_{14}O$ = 138.1045; found = 138.1045.

4-methylcyclohex-3-enecarbaldehyde



Colorless oil (64%);

R$_f$ = 0.65 (hexane/ethyl acetate, 4:1);

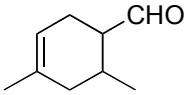
^{1}H NMR (300 MHz, $CDCl_3$): δ 1.64 (3H, s, -CH=C-C**H**$_3$), 1.94-2.49 (7H, m, -C**H**$_2$C-CHO, -C**H**-CHO, -C**H**$_2$-C**H**$_2$-C-CH$_3$), 5.38 (1H, brs, -C**H**=C-), 9.66 (1H, brs, -C**H**O);

^{13}C NMR (75 MHz, $CDCl_3$): δ 22.4 (-**C**H$_2$-), 23.4 (-**C**H$_3$), 24.4 (-**C**H$_2$-), 28.4 (-**C**H$_2$-), 45.8 (-**C**H-CHO), 118.6 (-C=**C**H-), 134.2 (-**C**=CH-), 204.6 (-**C**=O);

FTIR (neat, cm^{-1}): 2913, 1725, 1640;

HRMS (ESI [M$^+$]): calculated for $C_8H_{12}O$ = 124.0888; found = 124.0889.

4,6-dimethylcyclohex-3-enecarbaldehyde



Colorless oil (70%);

R$_f$ = 0.67 (hexane/ethyl acetate, 4:1);

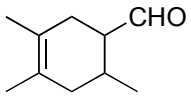
^{1}H NMR (300 MHz, $CDCl_3$): δ 1.02 (3H, d, *J* = 6.27 Hz, -C-C**H**$_3$), 1.64 (3H, s, -CH=C-C**H**$_3$), 2.02-2.18 (6H, m, -C**H**$_2$C-CHO, -C**H**-CHO, -C**H**-CH_3, -C**H**$_2$-C-CH_3), 5.37 (1H, brs, -C**H**=C-), 9.62 (1H, d, *J* = 2.79 Hz, -C**H**O);

^{13}C NMR (75 MHz, $CDCl_3$): δ 19.7 (-**C**H_3), 23.4 (-**C**H-CH_3), 24.1 (-**C**H_3), 28.3 (-**C**H_2-), 36.9 (-**C**H_2-), 52.3 (-**C**H-CHO), 117.8 (-C=**C**H-), 133.5 (-**C**=CH-), 205.4 (-**C**=O);

FTIR (neat, cm^{-1}): 2918, 1731, 1644;

HRMS (ESI [M^+]): calculated for $C_9H_{14}O$ = 138.1045; found = 138.1045.

3,4,6-trimethylcyclohex-3-enecarbaldehyde



Colorless oil (77%);

R_f = 0.64 (hexane/ethyl acetate, 4:1);

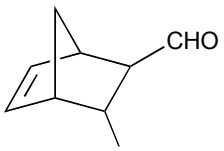
^{1}H NMR (300 MHz, $CDCl_3$): δ 0.99 (3H, d, *J* = 6.27 Hz, -C-C**H**$_3$), 1.59 (3H, s, -C=C-C**H**$_3$), 1.63 (3H, s, -C=C-C**H**$_3$), 1.85-2.16 (6H, m, -C**H**$_2$C-CHO, -C**H**-CHO, -C**H**-CH_3, -C**H**$_2$-C-CH_3), 9.60 (1H, d, *J* = 3.15 Hz, -C**H**O);

^{13}C NMR (75 MHz, $CDCl_3$): δ 18.6 (-**C**H_3), 18.8 (-**C**H_3), 19.5 (-**C**H_3), 28.7 (-**C**H-CH_3), 30.3 (-**C**H_2-), 38.9 (-**C**H_2-), 53.5 (-**C**H-CHO), 122.6 (-**C**=C-), 125.1 (-C=**C**-), 205.3 (-**C**=O);

FTIR (neat, cm^{-1}): 2918, 1725, 1641;

HRMS (ESI [M^+]): calculated for $C_{10}H_{16}O$ = 152.1201; found = 152.1200.

3-methylbicyclo[2.2.1]hept-5-ene-2-carbaldehyde



Colorless oil (52%);

R_f = 0.67 (hexane/ethyl acetate, 4:1);

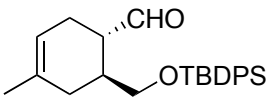
^{1}H NMR (300 MHz, $CDCl_3$): δ 1.17 (3H, d, *J* = 6.87 Hz, -C-C**H**$_3$), 1.43-1.61 (2H, m, -C**H**$_2$-), 1.77-1.85 (1H, m, -C**H**-CH$_3$), 2.22-2.34 (3H, m, -C**H**$_2$-, -C**H**-CHO), 2.55 (1H, brs, -C**H**-), 3.12 (1H, brs, -C**H**-), 6.04 (1H, dd, *J* = 5.91, 2.79 Hz, -C**H**=CH-), 6.29 (1H, dd, *J* = 5.55, 3.15 Hz, -C**H**=CH-), 9.37 (1H, d, *J* = 3.15 Hz, -C**H**O);

^{13}C NMR (75 MHz, $CDCl_3$): δ 20.7 (-**C**H$_3$), 36.2 (-**C**H-), 45.3 (-**C**H-), 46.1 (-**C**H$_2$-), 48.9 (-**C**H-), 61.2 (-**C**H-CHO), 132.5 (-HC=**C**H-), 138.9 (-H**C**=CH-), 204.9 (-**C**=O);

FTIR (neat, cm^{-1}): 2978, 1724;

HRMS [M^+]: calculated for $C_9H_{12}O$ = 136.0888; found = 136.0891.

6-(*tert*-Butyl-diphenyl-silanyloxymethyl)-3-methyl-cyclohex-3-enecarbaldehyde (62)



62

Yield = 83% ($BF_3.OEt_2$); 77% ($In(OTf)_3$);

R_f = 0.68 (Hexane:EtOAc, 8:1);

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.13 (9H, d, *J* = 0.9 Hz, -SiC(C**H**$_3$)$_3$), 1.66 (3H, s, -CH=C-C**H**$_3$), 1.78 (1H, dd, *J* = 17.57, 6.95 Hz, -CH=C-C**H**$_2$-), 2.01 (1H, dd, *J* = 17.57, 5.05 Hz, -CH=C-C**H**$_2$-), 2.12 (1H, brd, *J* = 17.55 Hz, -C=CH-C**H**$_2$-), 2.31 (1H, ddd, *J* = 17.55, 5.05, 2.3 Hz, -C=CH-C**H**$_2$-), 2.41 (1H, dq, *J* = 6.95, 6.45 Hz, -

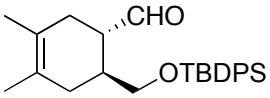
C**H**CH_2OTBDPS), 2.57 (1H, ddd, *J* = 6.95, 6.45, 2.8 Hz, -C**H**CHO), 3.64 (1H, dd, *J* = 9.25, 8.8 Hz, -C**H**$_2$OTBDPS), 3.72 (1H, dd, *J* = 9.25, 5.55 Hz, -C**H**$_2$OTBDPS), 5.42 (1H, brs, -C=C**H**CH_2), 7.43-7.47 (6H, m, Ph-**H**), 7.73-7.74 (4H, m, Ph-**H**), 9.76 (1H, d, *J* = 2.8 Hz, C**H**O) ppm;

^{13}C NMR (75 MHz, $CDCl_3$): δ 19.1 (-**C**$(CH_3)_3$), 23.2 (-C=CH-**C**H_2-), 23.3 (-CH=C-**C**H_3), 26.7 (-C(**C**$H_3)_3$), 30.4 (-CH=C-**C**H_2-), 36.4 (-**C**H-CH_2OTBDPS), 48.3 (-**C**H-CHO), 66.1 (-**C**H_2OTBDPS), 118.0 (-**C**H=C-CH_3), 127.6 (Ph-**C***m* x4), 129.6 (Ph-**C***p* x2), 132.7 (Ph-**C***q* x2), 133.2 (-CH=**C**-CH_3), 135.4 (Ph-**C***o* x4), 204.2 (**C**HO) ppm;

FTIR (neat, cm^{-1}): 3030, 2856, 1720, 1435;

HRMS (ESI [M+Na]$^+$): *m/e* calculated for $[C_{25}H_{32}NaO_2Si]^+$ = 415.2070; found = 415.2070.

6-(*tert*-Butyl-diphenyl-silanyloxymethyl)-3,4-dimethyl-cyclohex-3-enecarbaldehyde (63)



63

Yield = 75% ($BF_3.OEt_2$); 69% ($In(OTf)_3$);

R_f = 0.71 (Hexane:EtOAc, 8:1);

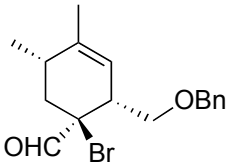
^{1}H NMR (300 MHz, $CDCl_3$): δ 1.07 (9H, s, -SiC(C**H**$_3)_3$), 1.58 (3H, s, -C=CC**H**$_3$), 1.64 (3H, s, -C=CC**H**$_3$), 1.76 (1H, dd, *J* = 16.98, 6.39 Hz, -C=CC**H**$_2$-), 1.95 (2H, brd, *J* = 16.98 Hz, -C=CC**H**$_2$-, -C=CC**H**$_2$-), 2.13-2.34 (2H, m, -C**H**CH_2OTBDPS, -C=CC**H**$_2$-), 2.48-2.55 (1H, m, -C**H**CHO), 3.55 (1H, dd, *J* = 10.44, 7.65 Hz, -C**H**$_2$OTBDPS), 3.65 (1H, dd, *J* = 10.44, 5.22 Hz, -C**H**$_2$OTBDPS), 7.37-7.44 (6H, m, Ph-**H**), 7.64-7.67 (4H, m, Ph-**H**), 9.70 (1H, d, *J* = 3.21 Hz, C**H**O) ppm;

^{13}C NMR (75 MHz, $CDCl_3$): δ 18.6 (-C=C-**C**H_3), 18.8 (-C=C-**C**H_3), 19.1 (-**C**$(CH_3)_3$), 26.7 (-C(**C**$H_3)_3$), 29.5 (-C=C-**C**H_2-), 32.3 (-C=C-**C**H_2-), 36.9 (-**C**H-CH_2OTBDPS), 49.6 (-**C**H-CHO), 66.3 (-**C**H_2OTBDPS), 122.9 (-C=**C**-CH_3), 124.4 (-C=**C**-CH_3), 127.6 (Ph-**C***m* x4), 129.6 (Ph-**C***p* x2), 133.3 (Ph-**C***q* x2), 135.5 (Ph-**C***o* x4), 204.4 (**C**HO) ppm;

FTIR (neat, cm^{-1}): 3069, 2856, 1724, 1427;

HRMS (ESI [M+Na]$^+$): *m/e* calculated for $[C_{26}H_{34}NaO_2Si]^+$ = 429.2226; found = 429.2221.

2-Benzyloxymethyl-1-bromo-4,5-dimethyl-cyclohex-3-enecarbaldehyde (64)



64

Yield = 94% ($BF_3.OEt_2$); 68% ($In(OTf)_3$);

R_f = 0.48 (Hexane:EtOAc, 4:1);

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.11 (3H, d, *J* = 6.95 Hz, -CHC**H**$_3$), 1.69 (1H, dd, *J* = 15.25, 10.15 Hz, -C**H**$_2$C-CHO), 1.73 (3H, d, *J* = 0.95 Hz, -CH=C-C**H**$_3$), 2.22 (1H, ddd, *J* = 15.25, 6.05, 1.85 Hz, -C**H**$_2$C-CHO), 2.44 (1H, brs, -C**H**CH_3), 3.06 (1H, t, *J* = 10.2 Hz, -C**H**$_2$OBn), 3.18 (1H, brs, -C**H**CH_2OBn), 3.40 (1H, dd, *J* = 10.2 Hz, 3.70 Hz, -C**H**$_2$OBn), 4.32 (1H, d, *J* = 11.55 Hz, -OC**H**$_2$Ph), 4.40 (1H, d, *J* = 11.55 Hz, -OC**H**$_2$Ph), 5.23 (1H, dt, *J* = 5.05, 1.35 Hz, -C**H**=CCH_3), 7.26-7.30 (3H, m, Ph-**H**), 7.33-7.36 (2H, m, Ph-**H**), 9.54 (1H, s, C**H**O) ppm;

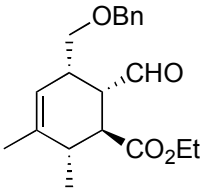
^{13}C NMR (125 MHz, $CDCl_3$): δ 18.8 (-CH-**C**H_3), 20.9 (-CH=C-**C**H_3), 32.9 (-**C**H-CH_3), 34.1 (-**C**H_2-C-CHO), 46.5 (-**C**H-CH_2OBn), 71.4 (-**C**H_2OBn), 72.3 (-**C**-CHO),

73.1 (-OCH_2Ph), 117.0 (-C=**C**H-), 127.8 (Ph-**C***p*), 127.8 (Ph-**C***o* x2), 128.4 (Ph-**C***m* x2), 137.2 (Ph-**C***q*), 140.7 (-CH=**C**-CH_3), 190.6 (**C**HO) ppm;

FTIR (neat, cm^{-1}): 3084, 3030, 2932, 2866, 1732, 1645,1454;

HRMS (EI [M^+-Br]): *m/e* calculated for $C_{17}H_{21}O_2$ = 257.1541; found = 257.1550.

ethyl 5-(benzyloxymethyl)-6-formyl-2,3-dimethylcyclohex-3-enecarboxylate (77b)



77b

Yield = 42%;

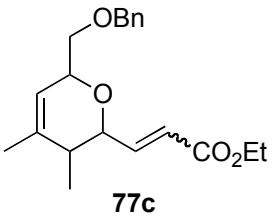
R_f = 0.44 (Hexane:EtOAc, 4:1);

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.09 (3H, d, *J* = 6.9 Hz, CHC**H**$_3$), 1.30 (3H, dd, *J* = 6.9, 7.4 Hz, -OCH_2C**H**$_3$), 1.67 (3H, d, *J* = 1.4 Hz, -CH=CC**H**$_3$), 2.25 (1H, dq, *J* = 7.9, 7.4 Hz, -C**H**CH_3), 2.50 (1H, dd, *J* = 10.2, 9.7 Hz, -C**H**CO_2Et), 3.03-3.09 (2H, m, -C**H**CHO, -C**H**CH_2OBn), 3.11 (1H, q, *J* = 8.8 Hz, -C**H**$_2$OBn), 3.40 (1H, dd, *J* = 8.8, 2.3 Hz, -C**H**$_2$OBn), 4.20 (2H, ddd, *J* = 14.3, 7.16, 1.4 Hz, -OC**H**$_2CH_3$), 4.30 (1H, d, *J* = 11.55 Hz, OC**H**$_2C_6H_5$), 4.40 (1H, d, *J* = 12 Hz, OC**H**$_2C_6H_5$), 5.38 (1H, d, *J* = 3.70, 1.35 Hz, -C**H**=C-), 7.26-7.35 (5H, m, OCH_2C_6**H**$_5$), 9.72 (1H, s, C**H**O) ppm;

^{13}C NMR (125 MHz, $CDCl_3$): δ 14.2 (-OCH_2**C**H_3), 17.5 (-CH-**C**H_3), 21.2 (-CH=C-**C**H_3), 36.7 (-**C**HCH_2OBn), 37.6 (-**C**H-CH_3), 44.2 (-**C**HCO_2Et), 52.1 (-**C**HCHO), 60.6 (-O**C**H_2CH_3), 70.3 (-CH-**C**H_2OBn), 73.0 (-O**C**H_2Ph), 120.1 (-**C**H=C-CH_3), 127.6 (Ph-**C***p*), 127.8 (Ph-**C***o* x2), 128.3 Ph-**C***m* x2), 137.6 (Ph-**C***q*), 139.5 (-CH=**C**-CH_3), 175.5 (**C**O_2Et), 200.9 (**C**HO) ppm;

HRMS (EI [M]$^+$): *m/e* calculated for $[C_{20}H_{26}O_4]^+$ = 330.1831, found = 330.1821.

ethyl 3-(6-(benzyloxymethyl)-3,4-dimethyl-3,6-dihydro-2*H*-pyran-2-yl)acrylate (77c)



77c

Yield = 41%;

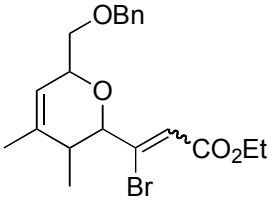
R_f = 0.48 (Hexane:EtOAc, 4:1);

^{1}H NMR (300 MHz, $CDCl_3$): δ 0.93 (3H, d, *J* = 6.96 Hz, CHC**H**$_3$), 1.29 (3H, t, *J* = 7.32 Hz, -OCH$_2$C**H**$_3$), 1.74 (3H, s, -C=CC**H**$_3$), 1.94-1.99 (1H, m, C**H**CH$_3$), 3.47 (1H, dd, *J* = 9.93, 4.71, Hz, -C**H**$_2$OBn), 3.55 (1H, dd, *J* = 10.11, 6.63 Hz, -C**H**$_2$OBn), 4.20 (2H, q, *J* = 7.32 Hz, -OC**H**$_2$CH$_3$), 4.29-4.32 (1H, m, -OC**H**CH=CH-), 4.37-4.40 (1H, m, -C**H**CH$_2$OBn), 4.58 (1H, d, *J* = 12.54 Hz, -OC**H**$_2$C$_6$H$_5$), 4.63 (1H, d, *J* = 12.54 Hz, -OC**H**$_2$C$_6$H$_5$), 5.32 (1H, s, -C**H**=C-), 6.14 (1H, dd, *J* = 15.66, 1.74 Hz, -CH=C**H**CO$_2$Et), 6.90 (1H, dd, *J* = 15.66, 3.84 Hz, -C**H**=CHCO$_2$Et), 7.26-7.35 (5H, m, -OCH$_2$C$_6$**H**$_5$) ppm;

^{13}C NMR (125 MHz, $CDCl_3$): δ 13.4 (-CH-**C**H$_3$), 14.2 (-OCH$_2$**C**H$_3$), 21.5 (-CH=C-**C**H$_3$), 37.4 (-**C**H-CH$_3$), 60.1 (-O**C**H$_2$CH$_3$), 73.1 (-CHCH$_2$O**C**H$_2$Ph), 73.3 (-CH**C**H$_2$OBn), 74.9 (-O**C**HCH$_2$OBn), 75.3 (-O**C**HCH=CHCO$_2$Et), 120.0 (-**C**H=C-CH$_3$), 120.8 (-CH=**C**HCO$_2$Et), 127.4 (Ph-**C***p*), 127.6 (Ph-**C***o* x2), 128.2 (Ph-**C***m* x2), 138.3 (-CH=**C**CH$_3$), 139.2 (Ph-**C***q*), 146.5 (-**C**H=CHCO$_2$Et), 166.5 (**C**O$_2$Et) ppm;

HRMS (EI $[M]^+$): *m/e* calculated for $[C_{20}H_{26}O_4]^+$ = 330.1831; found = 330.1828

Ethyl 3-(6-(benzyloxymethyl)-3,4-dimethyl-3,6-dihydro-2*H*-pyran-2-yl)-3-bromoacrylate (78c)



78c diastereomer

Yield = 56%;

Diastereomer 1:

R_f = 0.57 (Hexane:EtOAc, 4:1);

^{1}H NMR (500 MHz, $CDCl_3$): δ 0.90 (3H, d, *J* = 6.9 Hz, CHC**H**$_3$), 1.32 (3H, dd, *J* = 6.95, 6.90 Hz, -OCH$_2$C**H**$_3$), 1.78 (3H, s, -CH=CC**H**$_3$), 2.45 (1H, d, *J* = 6.9 Hz, -C**H**CH$_3$), 3.48 (1H, dd, *J* = 9.95, 4.65 Hz, -C**H**$_2$OBn), 3.55 (1H, dd, *J* = 9.95, 6.45 Hz, -C**H**$_2$OBn), 4.24 (2H, q, *J* = 6.95 Hz, -OC**H**$_2$CH$_3$), 4.30 (1H, brs, -C**H**CH$_2$OBn), 4.41 (1H, brs, -OC**H**C-Br), 4.61 (2H, s, -OC**H**$_2$C$_6$H$_5$), 5.33 (1H, s, -C**H**=C-), 6.83 (1H, s, -C=C**H**CO$_2$Et), 7.28-7.36 (5H, m, -OCH$_2$C$_6$**H**$_5$) ppm;

^{13}C NMR (125 MHz, $CDCl_3$): δ 12.4 (-CH**C**H$_3$), 14.2 (-OCH$_2$**C**H$_3$), 21.7 (-CH=C-**C**H$_3$), 35.7 (-**C**HCH$_3$), 60.4 (-O**C**H$_2$CH$_3$), 72.9 (-O**C**H$_2$Ph), 73.3 (-**C**H$_2$OBn), 75.7 (-O**C**HCH$_2$OBn), 80.4 (-O**C**HC=CHCO$_2$Et), 119.0 (-**C**H=C-), 119.7 (-C=**C**H-), 127.5 (Ph-**C***p*), 127.6 (Ph-**C***o* x2), 128.3 (Ph-**C***m* x2), 137.9 (**C***q*), 138.2 (**C***q*), 139.2 (**C***q*), 164.4 (-**C**O$_2$Et) ppm;

Diastereomer 2:

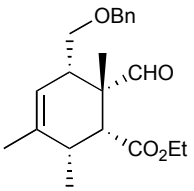
^{1}H NMR (500 MHz, $CDCl_3$): δ 1.05 (3H, d, *J* = 6.95 Hz, CHC**H**$_3$), 1.32 (3H, dd, *J* = 7.40, 6.95 Hz, -OCH$_2$C**H**$_3$), 1.75 (3H, s, -CH=CC**H**$_3$), 2.50 (1H, d, *J* = 6.9 Hz, -C**H**CH$_3$), 3.49 (1H, dd, *J* = 9.70, 4.15 Hz, -C**H**$_2$OBn), 3.57 (1H, dd, *J* = 9.70, 6.5 Hz, -C**H**$_2$OBn), 4.14 (1H, d, *J* = 5.55 Hz, -C**H**CH$_2$OBn), 4.23 (2H, q, *J* = 6.95 Hz, -

OC**H**$_2$CH$_3$), 4.39 (1H, brs, -OC**H**CBr-), 4.59 (2H, s, -OC**H**$_2$C$_6$H$_5$), 5.29 (1H, s, -C**H**=C-), 6.47 (1H, s, -C=C**H**CO$_2$Et), 7.28-7.35 (5H, m, -OCH$_2$C$_6$**H**$_5$) ppm;

^{13}C NMR (125 MHz, CDCl$_3$): δ 14.1 (-CH**C**H$_3$), 16.2 (-OCH$_2$**C**H$_3$), 21.2 (-CH=C-**C**H$_3$), 35.4 (-**C**HCH$_3$), 60.7 (-O**C**H$_2$CH$_3$), 71.7 (-O**C**HCH$_2$OBn), 72.0 (-O**C**H$_2$Ph), 73.2 (-**C**H$_2$OBn), 81.4 (-O**C**HC=CHCO$_2$Et), 119.9 (-**C**H=C-), 122.1 (-C=**C**H-), 127.6 (Ph-**C***p*), 127.8 (Ph-**C***o* x2), 128.3 (Ph-**C***m* x2), 135.8 (**C***q*), 138.2 (**C***q*), 139.6 (**C***q*), 164.1 (**C**O$_2$Et) ppm;

HRMS (EI [M]$^+$): *m/e* calculated for $[C_{20}H_{25}BrO_4]^+$ = 408.0936, found = 408.0920.

ethyl 5-(benzyloxymethyl)-6-formyl-2,3,6-trimethylcyclohex-3-enecarboxylate (79a)



79a

Yield = 35%

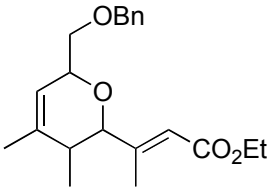
R$_f$ = 0.41 (Hexane:EtOAc, 4:1);

^{1}H NMR (500 MHz, CDCl$_3$): δ 1.06 (3H, d, *J* = 7.4 Hz, CHC**H**$_3$), 1.21(3H, s, -CC**H**$_3$), 1.26 (3H, dd, *J* = 7.4, 6.95 Hz, -OCH$_2$C**H**$_3$), 1.78 (3H, d, *J* = 0.95 Hz, -CH=CC**H**$_3$), 2.35 (1H, m, -C**H**CH$_2$OBn), 2.62 (1H, dq, *J* = 7.4, 6.95 Hz, -C**H**CH$_3$), 2.96 (1H, d, *J* = 6.45 Hz, -C**H**CO$_2$Et), 3.32 (1H, dd, *J* = 6.95, 6.95 Hz, -C**H**$_2$OBn), 3.55 (1H, dd, *J* = 9.25, 4.15 Hz, -C**H**$_2$OBn), 4.15 (2H, ddd, *J* = 14.32, 7.15, 0.95 Hz, -OC**H**$_2$CH$_3$), 4.40 (1H, d, *J* = 12.05 Hz, -OC**H**$_2$C$_6$H$_5$), 4.44 (1H, d, *J* = 12.00 Hz, -OC**H**$_2$C$_6$H$_5$), 5.47 (1H, d, *J* = 1.4 Hz, -C**H**=C-), 7.26-7.34 (5H, m, -OCH$_2$C$_6$**H**$_5$), 9.91 (1H, s, C**H**O) ppm;

^{13}C NMR (125 MHz, $CDCl_3$): δ 14.1 (-OCH_2**C**H_3), 16.4 (-CH-**C**H_3), 20.5 (-C-**C**H_3), 21.7 (-CH=C-**C**H_3), 34.9 (-**C**H-CH_3), 45.7 (-**C**H-CH_2OBn), 48.5 (-**C**-CHO), 54.6 (-**C**H-CO_2Et), 60.5 (-O**C**H_2CH_3), 69.9 (-CH-**C**H_2OBn), 73.1 (-CH-CH_2O**C**H_2Ph), 121.8 (-**C**H=C-CH_3), 127.5 (Ph-**C***p*), 127.6 (Ph-**C***o* x2), 128.3 (Ph-**C***m* x2), 135.6 (-CH=**C**-CH_3), 138.0 (Ph-**C***q*), 172.6 (-**C**O_2Et), 203.2 (**C**HO) ppm;

HRMS (EI $[M]^+$): *m/e* calculated for $[C_{21}H_{28}O_4]^+$ = 344.1988; found = 344.1988.

(*E*)-ethyl 3-(6-(benzyloxymethyl)-3,4-dimethyl-3,6-dihydro-2*H*-pyran-2-yl)but-2-enoate (79c)



79c

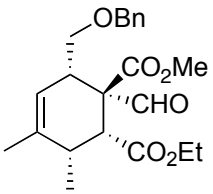
Yield = 9%;

R_f = 0.54 (Hexane:EtOAc, 4:1);

^{1}H NMR (300 MHz, $CDCl_3$): δ 0.85 (3H, d, *J* = 6.7 Hz, -C**H**$_3$), 1.30 (3H, t, *J* = 7.1 Hz, -OCH_2C**H**$_3$), 1.77 (3H, s, -C**H**$_3$), 2.11 (3H, s, -C**H**$_3$), 2.30-2.34 (1H, m, -C**H**CH_3), 3.49 (1H, dd, *J* = 10.1, 4.85, Hz, -C**H**$_2$OBn), 3.50 (1H, dd, *J* = 10.1, 6.25 Hz, -C**H**$_2$OBn), 4.06 (1H, brs, -OCH-), 4.14-4.21 (2H, m, -OC**H**$_2CH_3$), 4.37 (1H, brs, -OC**H**-), 4.43-4.51 (1H, m, -OC**H**-), 4.63 (2H, s, -OC**H**$_2C_6H_5$), 5.37 (1H, s, -C**H**=C-), 6.13 (1H, s, -CH=C**H**CO_2Et), 7.27-7.38 (5H, m, -OCH_2C_6**H**$_5$) ppm;

^{13}C NMR (125 MHz, $CDCl_3$): δ 12.9 (-**C**H_3), 14.4 (-**C**H_3), 15.9 (-**C**H_3), 21.8 (-**C**H_3), 35.8 (-**C**H-), 59.6 (-O**C**H-), 73.2 (-O**C**H-), 73.4 (-**C**H-), 75.2 (-O**C**H_2-), 79.4 (-O**C**H_2-), 115.1 (-**C**H=C-), 120.2 (-C=**C**H-), 127.6 (Ph-**C***p*), 127.7 (Ph-**C***o* x2), 128.4 (Ph-**C***m* x2), 138.4 (-CH=**C**-), 139.3 (Ph-**C***q*), 155.8 (-**C**=CH-), 167.1 (-**C**O_2Et) ppm;

2-ethyl 1-methyl 6-(benzyloxymethyl)-1-formyl-3,4-dimethylcyclohex-4-ene-1,2-dicarboxylate (88a)



88a

Yield = 22%

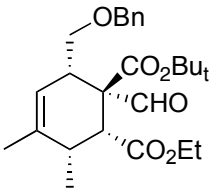
R_f = 0.30 (Hexane:EtOAc, 4:1);

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.21 (3H, d, *J* = 6.95 Hz, CHC**H**$_3$), 1.24 (3H, dd, *J* = 7.4, 6.95 Hz, -OCH$_2$C**H**$_3$), 1.69 (3H, s, -CH=CC**H**$_3$), 2.64 (1H, dq, *J* = 7.85, 6.95 Hz, -C**H**CH$_3$), 3.04 (1H, d, *J* = 9.25 Hz, -C**H**CO$_2$Et), 3.18 (1H, m, -C**H**CH$_2$OBn), 3.29 (1H, dd, *J* = 8.8, 8.3 Hz, 1H, -C**H**$_2$OBn), 3.45 (1H, dd, *J* = 10.17, 3.25 Hz, -C**H**$_2$OBn), 3.71 (3H, s, CO$_2$**Me**), 4.16 (2H, dd, *J* = 12.0, 7.4 Hz, -OC**H**$_2$CH$_3$), 4.35 (1H, d, *J* = 11.55 Hz, OC**H**$_2$C$_6$H$_5$), 4.41 (1H, d, *J* = 12.05 Hz, -OC**H**$_2$C$_6$H$_5$), 5.28 (1H, d, *J* = 6.05 Hz, -C**H**=C-), 7.26-7.35 (5H, m, -OCH$_2$C$_6$**H**$_5$), 9.89 (1H, s, C**H**O) ppm;

^{13}C NMR (125 MHz, $CDCl_3$): δ 13.9 (-OCH$_2$**C**H$_3$), 19.8 (-CH**C**H$_3$), 21.3 (-CH=C-**C**H$_3$), 34.3 (-**C**HCH$_3$), 42.0 (-**C**HCH$_2$OBn), 46.3 (-**C**HCO$_2$Et), 52.2 (-CO$_2$**Me**), 61.0 (-O**C**H$_2$CH$_3$), 61.9 (-**C**-CHO), 69.9 (-CH**C**H$_2$OBn), 72.8 (-CHCH$_2$O**C**H$_2$Ph), 117.8 (-**C**H=C-CH$_3$), 127.6 (Ph-C*p*), 127.7 (Ph-C*o* x2), 128.3 (Ph-C*m* x2), 137.4 (Ph-C*q*), 140.5 (-CH=**C**-CH$_3$), 170.6 (-**C**O$_2$Me), 173.0 (-**C**O$_2$Et), 198.1 (**C**HO) ppm;

HRMS (EI [M]$^+$): *m/e* calculated for $[C_{22}H_{28}O_6]^+$ = 388.1886, found = 388.1888.

1-*tert*-butyl 2-ethyl 6-(benzyloxymethyl)-1-formyl-3,4-dimethylcyclohex-4-ene-1,2-dicarboxylate (95a)



95a

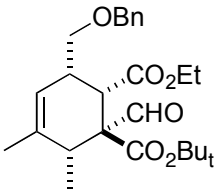
R_f = 0.31 (Hexane:EtOAc, 4:1);

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.22 (3H, d, *J* = 6.9 Hz, -CHC**H**$_3$), 1.26 (3H, t, *J* = 7.2 Hz, -OCH$_2$C**H**$_3$), 1.43 (9H, s, -OC(C**H**$_3$)$_3$), 1.71 (3H, s, -CH=CC**H**$_3$), 2.64 (1H, dq, *J* = 14.1, 7.2 Hz, -C**H**-), 3.05 (1H, d, *J* = 9.0 Hz, -C**H**-), 3.17 (1H, brs , -C**H**CO$_2$Et), 3.32 (1H, dd, *J* = 10.5, 8.4 Hz, 1H, -C**H**$_2$OBn), 3.44 (1H, dd, *J* = 10.5, 3.9 Hz, -C**H**$_2$OBn), 4.17 (2H, q, *J* = 7.2 Hz, -OC**H**$_2$CH$_3$), 4.38 (1H, d, *J* = 12.0 Hz, -OC**H**$_2$C$_6$H$_5$), 4.44 (1H, d, *J* = 12.0 Hz, -OC**H**$_2$C$_6$H$_5$), 5.34 (1H, d, *J* = 6.0 Hz, -C**H**=C-), 7.28-7.37 (5H, m, -OCH$_2$C$_6$**H**$_5$), 9.89 (1H, s, C**H**O) ppm;

^{13}C NMR (125 MHz, $CDCl_3$): δ 14.0 (-OCH$_2$**C**H$_3$), 20.2 (-CH**C**H$_3$), 21.3 (-CH=C-**C**H$_3$), 27.8 (-C(**C**H$_3$)$_3$), 34.6 (-**C**HCH$_3$), 42.2 (-**C**HCH$_2$OBn), 46.3 (-**C**HCO$_2$Et), 60.8 (-**C**-CHO),), 62.2 (-O**C**H$_2$CH$_3$), 70.0 (-CH**C**H$_2$OBn), 72.8 (-CHCH$_2$O**C**H$_2$Ph), 82.1 (-O**C**(CH$_3$)$_3$), 118.4 (-**C**H=C-CH$_3$), 127.7 (Ph-C*p*), 127.8 (Ph-C*o* x2), 128.3 (Ph-C*m* x2), 137.6 (Ph-C*q*), 140.3 (-CH=**C**-CH$_3$), 169.2 (-**C**O$_2$Bu$_t$), 173.0 (-**C**O$_2$Et), 198.9 (**C**HO) ppm;

HRMS (EI [M]$^+$): *m/e* calculated for $[C_{22}H_{28}O_6]^+$ = 388.1886, found = 388.1888.

1-*tert*-butyl 2-ethyl 3-(benzyloxymethyl)-1-formyl-5,6-dimethylcyclohex-4-ene-1,2-dicarboxylate (95d)



95d

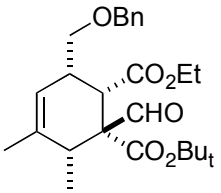
R_f = 0.35 (Hexane:EtOAc, 4:1);

^{1}H NMR (300 MHz, $CDCl_3$): δ 0.87 (3H, d, *J* = 7.2 Hz, -CHC**H**$_3$), 1.30 (3H, dd, *J* = 7.2, 6.9 Hz, -OCH$_2$C**H**$_3$), 1.40 (9H, s, -OC(C**H**$_3$)$_3$), 1.70 (3H, s, -CH=CC**H**$_3$), 2.64-2.73 (2H, m, -C**H**CH$_3$, -C**H**CH$_2$OBn), 3.51 (1H, d, *J* = 6.3 Hz, -C**H**CO$_2$Et), 3.59 (1H, dd, *J* = 9.3, 3.9 Hz, 1H, -C**H**$_2$OBn), 3.79 (1H, t, *J* = 9 Hz, -C**H**$_2$OBn), 4.21 (2H, ddd, *J* = 9.9, 7.2, 2.7 Hz, -OC**H**$_2$CH$_3$), 4.45 (1H, d, *J* = 12.3 Hz, OC**H**$_2$C$_6$H$_5$), 4.53 (1H, d, *J* = 12.3 Hz, -OC**H**$_2$C$_6$H$_5$), 5.53 (1H, brs, -C**H**=C-), 7.22-7.32 (5H, m, -OCH$_2$C$_6$**H**$_5$), 10.11 (1H, d, *J* = 1.5 Hz, C**H**O) ppm;

^{13}C NMR (125 MHz, $CDCl_3$): δ 14.1 (-OCH$_2$**C**H$_3$), 14.8 (-CH**C**H$_3$), 21.2 (-CH=C-**C**H$_3$), 27.7 (-C(**C**H$_3$)$_3$), 34.7 (-**C**HCH$_3$), 43.4 (-**C**HCH$_2$OBn), 52.4 (-**C**HCO$_2$Et), 59.1 (-**C**-CHO),), 60.9 (-O**C**H$_2$CH$_3$), 70.3 (-CH**C**H$_2$OBn), 72.9 (-CHCH$_2$O**C**H$_2$Ph), 82.8 (-O**C**(CH$_3$)$_3$), 121.7 (-**C**H=C-CH$_3$), 127.4 (Ph-C*p*), 127.6 (Ph-C*o* x2), 128.2 (Ph-C*m* x2), 134.5 (Ph-C*q*), 138.2 (-CH=**C**-CH$_3$), 170.7 (-**C**O$_2$But), 172.5 (-**C**O$_2$Et), 199.3 (**C**HO) ppm;

HRMS (EI $[M]^+$): *m/e* calculated for $[C_{22}H_{28}O_6]^+$ = 388.1886, found = 388.1888.

1-*tert*-butyl 2-ethyl 3-(benzyloxymethyl)-1-formyl-5,6-dimethylcyclohex-4-ene-1,2-dicarboxylate (95e)



95e

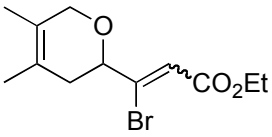
R_f = 0.35 (Hexane:EtOAc, 4:1);

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.18 (3H, dd, *J* = 7.2, 6.9 Hz, -$OCH_2C\mathbf{H}_3$), 1.19 (3H, d, *J* = 7.2 Hz, -$CHC\mathbf{H}_3$), 1.49 (9H, s, -$OC(C\mathbf{H}_3)_3$), 1.78 (3H, s, -$CH{=}CC\mathbf{H}_3$), 2.53-2.61 (1H, m, -$C\mathbf{H}CH_3$) 2.97-3.07 (1H, m, -$C\mathbf{H}CH_2OBn$), 3.24-3.39 (2H, m, -$C\mathbf{H}_2OBn$), 3.55 (1H, d, *J* = 6.6 Hz, -$C\mathbf{H}CO_2Et$), 3.88 (1H, dq, *J* = 10.8, 7.2 Hz, -$OC\mathbf{H}_2CH_3$), 4.06 (1H, dq, *J* = 10.5, 6.9 Hz, -$OC\mathbf{H}_2CH_3$), 4.37 (1H, d, *J* = 12.0 Hz, -$OC\mathbf{H}_2C_6H_5$), 4.41 (1H, d, *J* = 12.0 Hz, -$OC\mathbf{H}_2C_6H_5$), 5.35 (1H, brs, -C**H**=C-), 7.26-7.35 (5H, m, -$OCH_2C_6\mathbf{H}_5$), 10.15 (1H, d, *J* = 1.5 Hz, C**H**O) ppm;

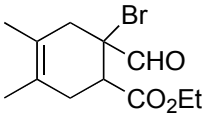
^{13}C NMR (125 MHz, $CDCl_3$): δ 13.3 (-$OCH_2\mathbf{C}H_3$), 13.9 (-$CH\mathbf{C}H_3$), 21.4 (-CH=C-$\mathbf{C}H_3$), 27.8 (-$C(\mathbf{C}H_3)_3$), 37.5 (-$\mathbf{C}HCH_3$), 39.5 (-$\mathbf{C}HCH_2OBn$), 48.9 (-$\mathbf{C}HCO_2Et$), 60.8 (-**C**-CHO),), 61.3 (-$O\mathbf{C}H_2CH_3$), 70.9 (-$CH\mathbf{C}H_2OBn$), 73.0 (-$CHCH_2O\mathbf{C}H_2Ph$), 82.8 (-$O\mathbf{C}(CH_3)_3$), 119.8 (-$\mathbf{C}H{=}C\text{-}CH_3$), 127.5 (Ph-C*p*), 127.7 (Ph-C*o* x2), 128.2 (Ph-C*m* x2), 136.8 (Ph-C*q*), 138.0 (-CH=**C**-CH_3), 170.9 (-$\mathbf{C}O_2Bu_t$), 172.6 (-$\mathbf{C}O_2Et$), 199.8 (**C**HO) ppm;

HRMS (EI $[M]^+$): *m/e* calculated for $[C_{22}H_{28}O_6]^+$ = 388.1886, found = 388.1888.

(entry 1, Table 2-9)



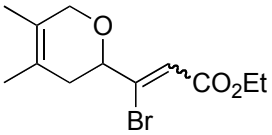
Hetero-Diels-Alder



Normal Diels-Alder

Yield = 95% (hetero : normal = 2:1);

ethyl 3-bromo-3-(4,5-dimethyl-3,6-dihydro-2*H*-pyran-2-yl)acrylate (entry 1, Table 2-9)

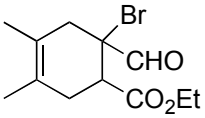


R_f = 0.51 (Hexane:EtOAc, 4:1);

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.28 (3H, t, *J* = 6.95 Hz, -$OCH_2C\mathbf{H}_3$), 1.63 (6H, d, *J* = 2.3 Hz, -$H_3CC{=}CC\mathbf{H}_3$-, -$\mathbf{H}_3CC{=}CCH_3$-), 2.11 (1H, d, *J* = 17.1 Hz, -C=CC$\mathbf{H}_2$CH-), 2.29 (1H, d, *J* = 17.1 Hz, -C=CC$\mathbf{H}_2$CH-), 4.07 (2H, brs, -CHOC$\mathbf{H}_2$-), 4.13-4.17 (-C**H**OCH_2-), 4.20 (2H, q, *J* = 6.95 Hz, -OC$\mathbf{H}_2CH_3$), 6.70 (1H, d, *J* = 0.9 Hz, -C=C**H**-);

^{13}C NMR (125 MHz, $CDCl_3$): δ 13.6 (-**C**H_3), 14.1 (-**C**H_3), 18.2 (-**C**H_3), 35.6 (-**C**H_2-), 60.5 (-O**C**H_2CH_3), 70.0 (-**C**H_2-O-), 78.2 (-O**C**H-), 118.3 (-**C**H=C-Br), 123.0 (-**C**=C-), 124.1 (-C=**C**-), 139.6 (-CH=**C**-Br), 164.4 (-**C**O_2Et) ppm;

ethyl 6-bromo-6-formyl-3,4-dimethylcyclohex-3-enecarboxylate (entry 1, Table 2-9)



R_f = 0.51 (Hexane:EtOAc, 4:1);

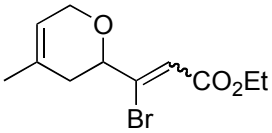
^{1}H NMR (500 MHz, $CDCl_3$): δ 1.26 (3H, t, *J* = 6.95 Hz, -$OCH_2C\mathbf{H}_3$), 1.63 (6H, d, *J* = 2.3 Hz, -$H_3CC{=}CC\mathbf{H}_3$-, -$\mathbf{H}_3CC{=}CCH_3$-), 2.11 (1H, d, *J* = 17.1 Hz, -C=CC$\mathbf{H}_2$CH-),

2.29 (1H, d, *J* = 17.1 Hz, -C=CC**H**$_2$CH-), 2.58 (1H, d, *J* = 18.25 Hz, -C**H**$_2$CCHO), 2.82 (1H, d, *J* = 18.25 Hz, -C**H**$_2$CCHO), 3.12 (1H, dd, *J* = 7.85, 7.40 Hz, -C**H**CO$_2$Et), 4.20 (2H, q, *J* = 6.95 Hz, -OC**H**$_2$CH$_3$), 9.64 (1H, s, C**H**O) ppm;

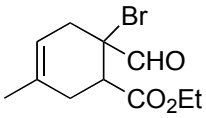
^{13}C NMR (125 MHz, CDCl$_3$): δ 14.0 (-**C**H$_3$), 18.1 (-**C**H$_3$), 18.3 (-**C**H$_3$), 32.3 (-**C**H$_2$-), 41.2 (-**C**H$_2$-), 46.5 (-**C**H-CO$_2$Et), 61.2 (-O**C**H$_2$CH$_3$), 68.3 (-**C**-CHO), 121.9 (-**C**=C-), 123.6 (-C=**C**-), 170.8 (-**C**O$_2$Et), 195.7 (-**C**HO) ppm;

HRMS (EI [M]$^+$): *m/e* calculated for [C$_{12}$H$_{17}$BrO$_3$]$^+$ = 288.0361, found = 288.0347.

entry 2, Table 2-9



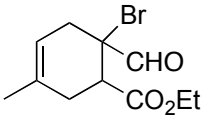
Hetero-Diels-Alder



Normal Diels-Alder

Yield = 58% (hetero : normal = 8:1)

ethyl 6-bromo-6-formyl-3-methylcyclohex-3-enecarboxylate (entry 2, Table 2-9)

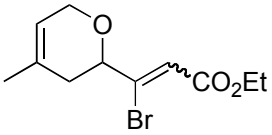


R$_f$ = 0.53 (Hexane:EtOAc, 4:1);

^{1}H NMR (300 MHz, CDCl$_3$): δ 1.28 (3H, t, *J* = 6.96 Hz, -OCH$_2$C**H**$_3$), 1.72 (3H, s, -H$_3$CC=CC**H**$_3$-), 1.98-2.29 (2H, m, -C=CC**H**$_2$CH-), 2.56-2.80 (2H, m, -C**H**$_2$CCHO), 3.18 (1H, dd, *J* = 7.65, 7.32 Hz, -C**H**CO$_2$Et), 4.11-4.25 (2H, m, -OC**H**$_2$CH$_3$), 5.28 (1H, brs, -**H**C=C-), 9.67 (1H, s, C**H**O) ppm;

^{13}C NMR (125 MHz, CDCl$_3$): δ 195.9 (-**C**HO) ppm;

ethyl 3-bromo-3-(4-methyl-3,6-dihydro-2*H*-pyran-2-yl)acrylate (entry 2, Table 2-9)

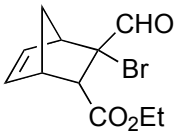


R_f = 0.53 (Hexane:EtOAc, 4:1);

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.28 (3H, t, *J* = 6.95 Hz, -$OCH_2C\mathbf{H}_3$), 1.72 (3H, s, -$HC{=}CC\mathbf{H}_3$-), 1.97-2.15 (2H, m, -$C{=}CC\mathbf{H}_2CH$-), 4.20 (2H, q, *J* = 6.95 Hz, -$OC\mathbf{H}_2CH_3$), 4.12-4.29 (3H, m, -$C\mathbf{H}OCH_2$-, -$CHOC\mathbf{H}_2$-), 5.42 (1H, brs, -**H**C=C-), 6.73 (1H, d, *J* = 1.4 Hz, -C=C**H**CO_2Et-);

^{13}C NMR (125 MHz, $CDCl_3$): δ 14.1 (-$OCH_2\mathbf{C}H_3$), 22.7 (-CH=C-$\mathbf{C}H_3$), 34.9 (-$\mathbf{C}H_2$-CH-O-), 60.5 (-$O\mathbf{C}H_2CH_3$), 66.3 (-$\mathbf{C}H_2$-O-), 77.8 (-O**C**H-), 118.4 (-**C**H=C-Br), 119.2 (-**C**H=C-CH_3-), 131.2 (-C=**C**-CH_3), 139.5 (-CH=**C**-Br), 164.4 (-$\mathbf{C}O_2$Et) ppm;

ethyl 3-bromo-3-formylbicyclo[2.2.1]hept-5-ene-2-carboxylate (entry 3, Table 2-9)



Yield = 72% (*endo* : *exo* = 11 : 89)

R_f = 0.55 (Hexane:EtOAc, 4:1);

major (*exo*): ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.22 (3H, dd, *J* = 6.9, 7.32 Hz, -$OCH_2C\mathbf{H}_3$), 1.33 (1H, d, *J* = 9.39 Hz, -$CHC\mathbf{H}_2CH$-), 1.60 (1H, d, *J* = 9.39 Hz, -$CHC\mathbf{H}_2CH$-), 3.15 (1H, s, -$CHCH_2C\mathbf{H}$-), 3.29 (1H, s, -$C\mathbf{H}CH_2CH$-), 3.67 (1H, d, *J* = 3.12 Hz, -C**H**-CO_2Et), 4.11 (2H, q, *J* = 6.97 Hz, -$OC\mathbf{H}_2CH_3$), 6.11 (1H, dd, *J* = 5.58, 3.12 Hz, -C**H**=CH-), 6.68 (1H, dd, *J* = 5.58, 3.12 Hz, -CH=C**H**-), 9.51 (1H, s, C**H**O) ppm;

^{13}C NMR (75 MHz, $CDCl_3$): δ 14.1 (-OCH_2**C**H_3), 44.6 (-**C**H-), 45.5 (-**C**H_2-), 49.2 (-**C**H-), 50.2 (-**C**H-), 60.8 (-O**C**H_2CH_3), 75.2 (-**C**-CHO), 133.1 (-**C**H=CH-), 139.7 (-CH=**C**H-), 170.3 (-**C**O_2Et), 190.3 (**C**HO) ppm;

minor (*endo*): ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.26 (3H, dd, *J* = 6.9, 7.32 Hz, -OCH_2C**H**$_3$), 1.33 (1H, d, *J* = 9.39 Hz, -CHC**H**$_2$CH-), 1.60 (1H, d, *J* = 9.39 Hz, -CHC**H**$_2$CH-), 3.15 (1H, s, -$CHCH_2$C**H**-), 3.29 (1H, s, -C**H**CH_2CH-), 3.67 (1H, d, *J* = 3.12 Hz, -C**H**-CO_2Et), 4.18 (2H, q, *J* = 7.29 Hz, -OC**H**$_2CH_3$), 6.01 (1H, dd, *J* = 5.58, 3.15 Hz, -C**H**=CH-), 6.29 (1H, dd, *J* = 5.58, 3.15 Hz, -CH=C**H**-), 9.33 (1H, s, C**H**O) ppm;

^{13}C NMR (75 MHz, $CDCl_3$): δ 14.1 (-OCH_2**C**H_3), 46.0 (-**C**H-), 47.9 (-**C**H_2-), 48.9 (-**C**H-), 53.0 (-**C**H-), 61.1 (-O**C**H_2CH_3), 75.2 (-**C**-CHO), 133.4 (-**C**H=CH-), 140.5 (-CH=**C**H-), 170.3 (-**C**O_2Et), 188.7 (**C**HO) ppm;

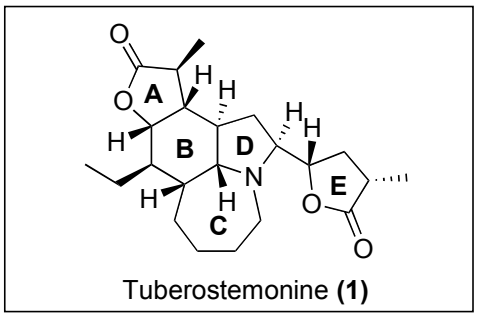
HRMS (EI $[M]^+$): *m/e* calculated for $[C_{11}H_{13}BrO_3]^+$ = 272.0048; found = 272.0036.

Chapter 3

Synthetic Studies Towards the Total Synthesis of Tuberostemonine

3.1 Introduction

Tuberostemonine (**1**) is the prototype of *Stemona* alkaloids isolated from *Stemonaceae* species.[1] The chemical investigation of *Stemona* alkaloids was initiated by their use in Chinese and Japanese folk medicine in the treatment of respiratory diseases such as pulmonary tuberculosis and bronchitis as well as insecticides.[2] Especially the tuberous roots of *S. tuberosa*, *S. japonica* and *S. sessilifolia* have a long history of usage in the Chinese and Japanese traditional medicine. The extracts from the fleshy tuberous roots are still used in the treatment of respiratory disorders, including pulmonary tuberculosis and bronchitis, but are also recommended against different insect pests or *ecto* - and *endo*-parasites.[3] The basic methanolic extracts obtained from fresh leaves of *Stemona japonica* showed strong activity against silkworm larvae.[4]



Tuberostemonine **(1)**

Figure 3-1

[1] (a) Gotz, M.; Edwards, O. E. in *The Alkaloids, Vol. IX*, Academic Press, New York, **1967**, p. 545. (b) Gotz, M.; Strunz, G. M. in *Alkaloids*: *MTP International Review of Sciences, Series One, Vol. IX*, Butterworth, London, **1973**, p. 143. (c) Shinozaki, H.; Ishida, M. *Brain. Res.* **1985**, *334*, 33.

[2] (a) Uyeo, S.; Irie, H.; Harada, H. *Chem. Pharm. Bull*. **1967**, *15*, 768. (b) Harada, H,; Irie, H.; Masaki, N.; Osaki, K.; Uyeo, S. *Chem. Commun*. **1967**, 460. (c) Edwards, O. E.; Feniak, G.; Handa, K. L. *Can. J. Chem.* **1962**, *40*, 455. (d) Lin, W. H.; Ye, Y.; Xu, R. S. *J. Nat. Prod.* **1992**, *55*, 571. (e) Brem, B.; Seger, C.; Pacher, P.; Hofer, O.; Vajrodaya, S.; Gerger, H. *J. Agric. Food Chem*. **2002**, *50*, 6383-6388. (f) Maruyama, M.; Takeda, K. *Comp. Biochem. Physiol., C: Pharmacol., Toxicol. Endocrinol.* **1994**, *107C*, 105-110.

[3] Terada, M.; Sano, M.; Ishii, A. I.; Kino, H.; Fukushima, S.; Noro, T. *Nippon Yakurigku Zasshi* **1982**, *79*, 93-103.

[4] Sakata, K.; Aoki, K.; Chang, C. F.; Sakura, A.; Tamura, S.; Murakoshi, S. *Agric. Biol. Chem*. **1978**, *42*, 457.

Tuberostemonine (**1**) was the first *Stemona* alkaloid belonging to the group of stenine (**3**) to have its biological activity tested, and its anthelmintics activity was detected when tested against *Angiostrogylus cantonensis*, *Dipylidium caninum* and *Fasciola hepatica* with an effect on the motility of these helminthic worms.[1a]

It was also found that tuberostemonine (**1**) depressed glutamate-induced responses at the crayfish neuromuscular junction at similar concentration to those of established glutamate inhibitors.[2f] These pharmacological properties indicate that some of the effects of the crude extracts may be attributed to tuberostemonine (**1**) and that this alkaloid may be a useful tool in the field of neuropharmacology.

The genus *Stemona (Stemonaceae)* is known as a rich source of structurally complex alkaloids with mainly saturated ring systems of unknown biogenetical origin. Pili and coworkers[5] have separated the *Stemona* alkaloids into five groups according to their structural features, i.e. stenine (**3**), stemoamide (**4**), tuberostemo-spironine (**5**), stemonamine (**6**), tuberostemonamide (**7**) as shown in Figure 3-2.

[1a] Gotz, M.; Edwards, O. E. in *The Alkaloids*, Vol. IX, Academic Press, New York, **1967**, p.545.

[5] (a) Pili, R. A.; de oliveira, M. C. F. *Nat. Prod. Rep.* **2000**, *17*, 117-127. (b) Xu, R. S.; Lu, Y. J.; Chu, J. H.; Iwashita, T.; Naoki, H.; Naya, Y.; Nakanishi, K.; *Tetrahedron* **1982**, *38*, 2667. (c) Lin, W.; Ye, Y.; Xu, R. *Chem. Abstr.* **1992**, *116*, 148183w. (d) Ky, P. T.; Kim, V. N.; Dung, N. X. *Chem. Abstr.* **1992**, *117*, 108076c. (e) Ye, Y.; Qin, G. W.; Xu, R. S. *J. Nat. Prod.* **1994**, *57*, 665. (f) Ye, Y.; Qin, G. W.; Xu, R. S. *Phytochemistry* **1994,** *37*, 1205. (g) Qin, G. W.; Xu, R. S. *Med. Res. Rev.* **1998**, *18*, 375.

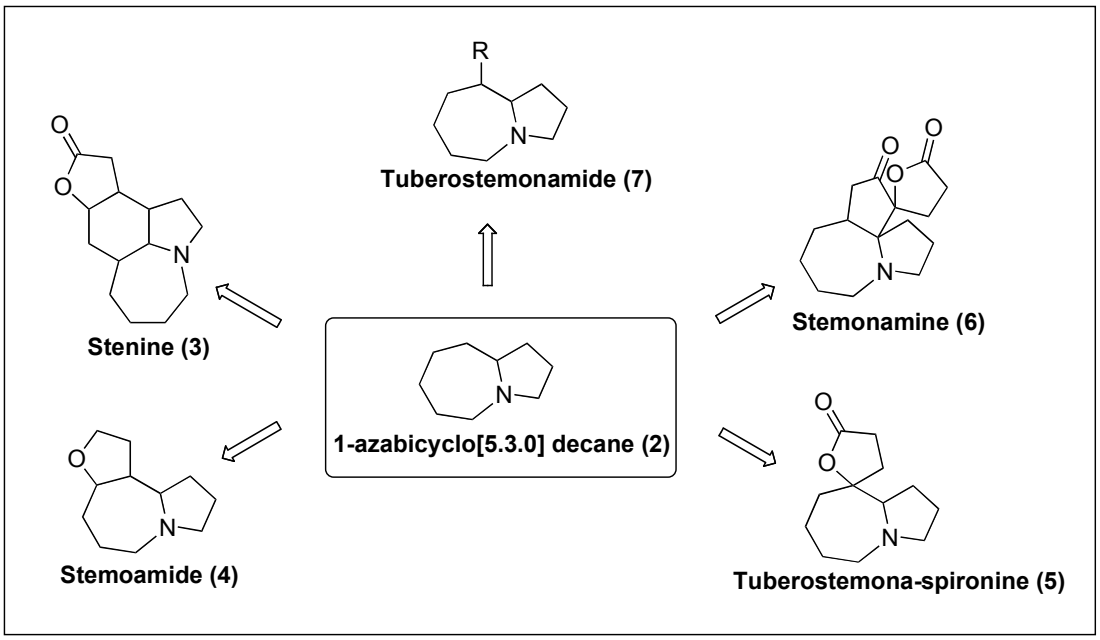


Figure 3-2

So far, more than 50 alkaloids of this family have been isolated, presenting a large structural diversity. Nevertheless, all the *Stemona* alkaloids are polycyclic and almost all present a common structural feature - a nucleus of 1-azabicyclo[5.3.0]decane (**2**). Most of them contain also one or more substructures of α-methyl-γ-butyrolactone, bound to the azabicyclic core either in spiranic or fused form or as a substituent of the pyrrolidine. All the *Stemona* alkaloids have several stereogenic centers. Their peculiar and complex structures, along with their potential bioactivity make them extremely attractive as synthetic targets. To date, there are several reports on the total synthesis of stenine (**3**) and recently a first total synthesis of tuberostemonine (**1**) has reported.

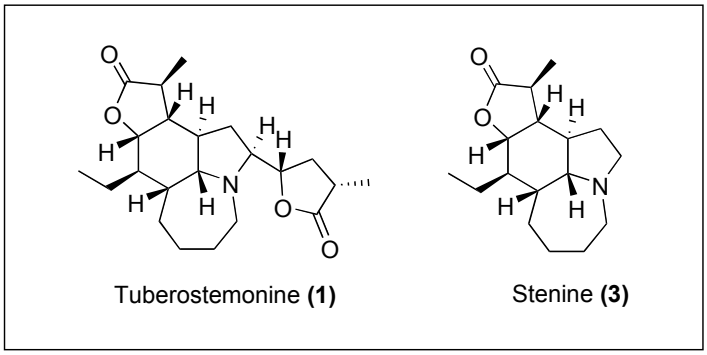
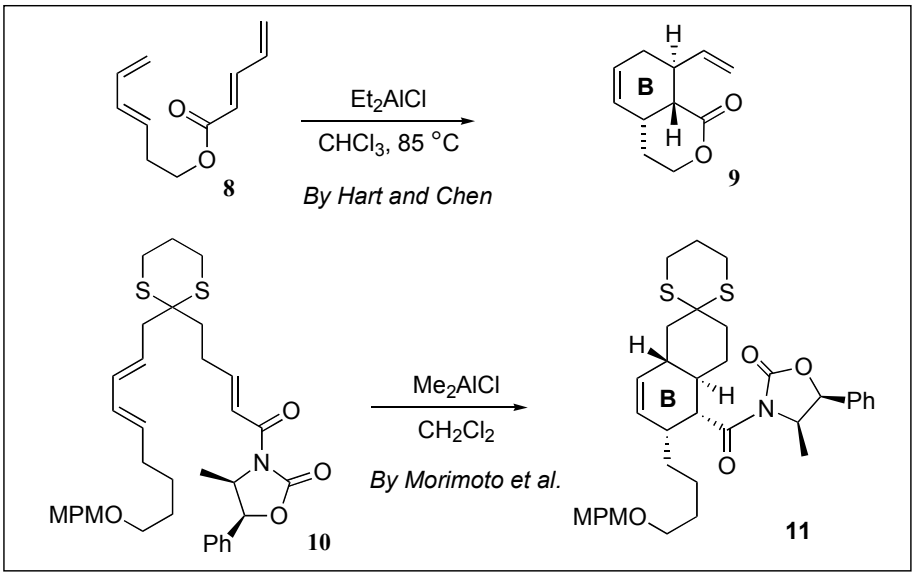


Figure 3-3

3.2 Previous Synthetic Works

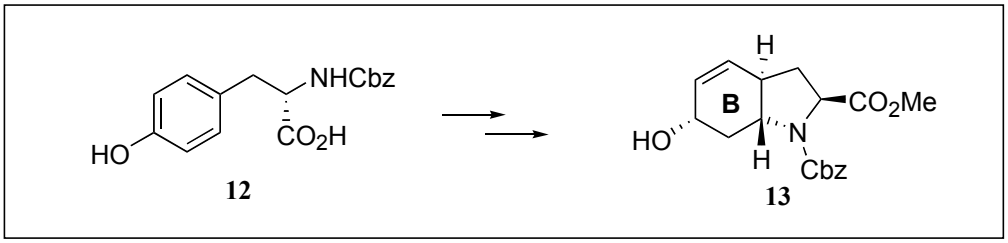
In general, strategies used in previous total synthesis of stenine (**3**) can be classified into two categories:

1. The highly functionalized six-membered ring B with the pre-requisite stereochemistry of the substituents is formed through an intramolecular Diels-Alder reaction catalyzed by Lewis acids, either thermally or at lower temperatures (Scheme 3-1).



Scheme 3-1

2. Functionalization of readily available six-membered ring to generate the chemical moieties of Ring B (Scheme 3-2).

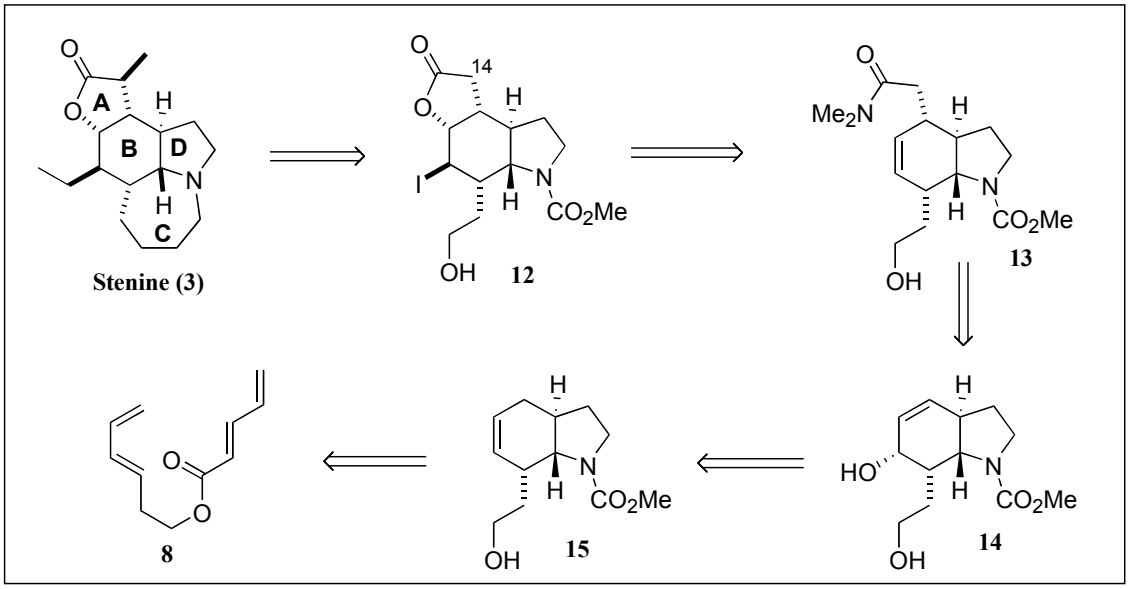


Scheme 3-2

3.2.1 Strategy 1: Intramolecular Diels-Alder Reaction for the Formation of Multifunctionalized Ring B

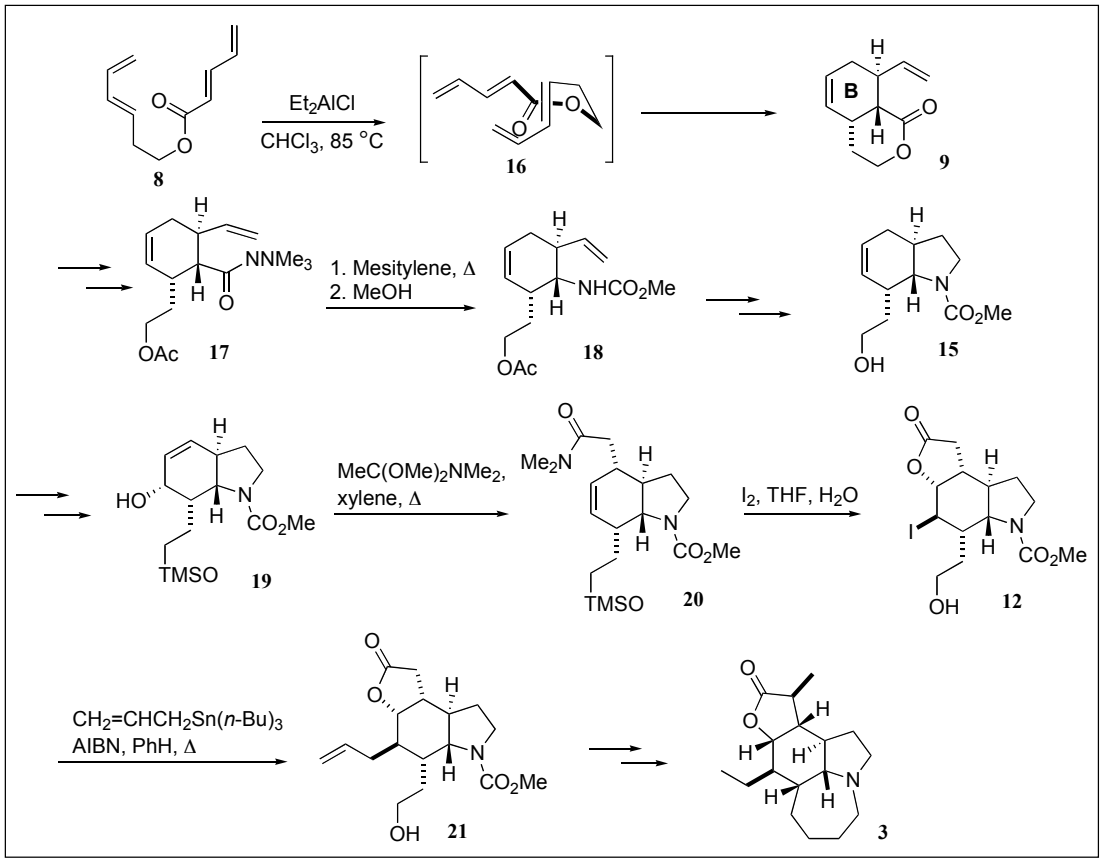
The total synthesis of stenine (**3**) was attempted by Hart and Chen in 1990.[6] They envisaged that iodolactone **12** would be a reasonable precursor for stenine (**3**) (Scheme 3-3). They planned to form the seven membered ring at the later stages of the synthesis. The C-14 methyl group was to be introduced using an alkylation, while the ethyl group was to be introduced using intermolecular free-radical carbon-carbon bond-forming reaction. It was anticipated that iodolactone **12** would be prepared from the tertiary amide **13**, which in turn would be prepared from **14** using an Eschenmoser-Claisen rearrangement. The terminal hydroxyl group in intermediate **15** was to serve as a handle for introducing the cyclohexenol moiety in intermediate **14**, and the cyclohexene ring in **15** was to be constructed using an intramolecular Diels-Alder reaction.

[6] (a) Chen, C. Y.; Hart, D. J. *J. Org. Chem.* **1990**, *55*, 6236. (b) Chen, C. Y.; Hart, D. J. *J. Org. Chem.* **1993**, *58*, 3840-3849.



Scheme 3-3

As shown in Scheme 3-4, the six membered ring B (**9**) was made from intramolecular Diels-Alder reaction of **8** catalyzed by diethylaluminium chloride in chloroform at 85 °C as a single stereoisomer. The nitrogen was introduced through a Curtius rearrangement of **17** to carbamate **18**. Then, it was followed by Eschenmoser-Claisen rearrangement of **19** to **20** and stereoselective free radical allylation of **12** to **21**.



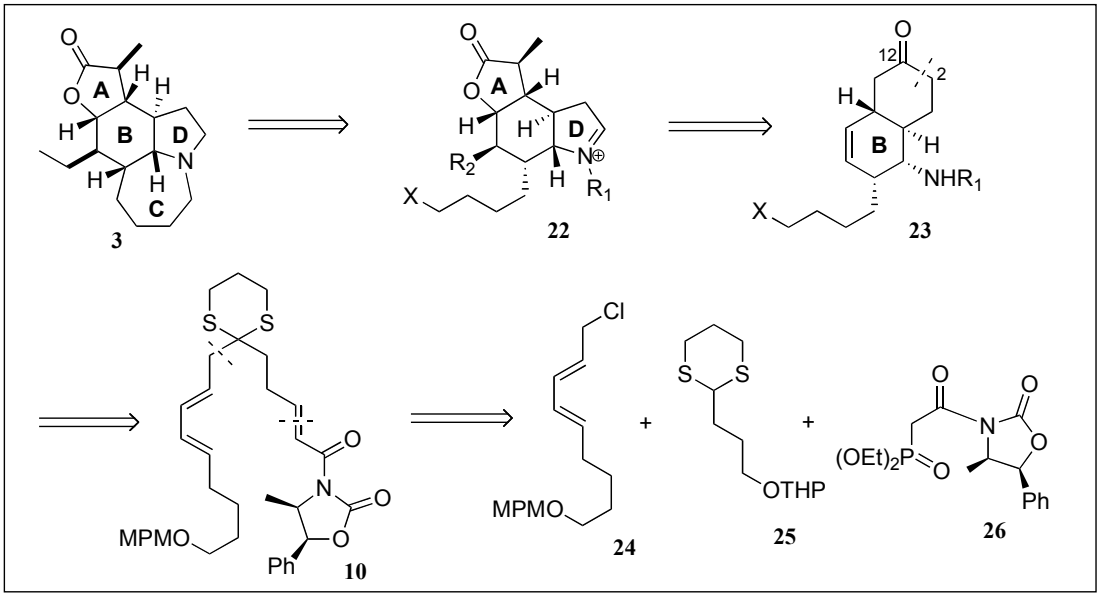
Scheme 3-4

Morimoto and co-workers (1996) have also applied the intramolecular Diels-Alder cycloaddition in an asymmetric synthesis of (-)-stenine as shown in Scheme 3-5.[7] They planned to construct the seven-membered ring in the last step of the synthesis through an intramolecular *N*-alkylation of the corresponding deprotected amine **22**. It was anticipated that tricyclic ring system **22** would be prepared from the bicyclic ketone **23** by oxidative cleavage of the C_2-C_{12} bond, followed by cyclization of A and D rings.

An intramolecular asymmetric Diels-Alder reaction of (*E*,*E*,*E*)-triene **10**, containing Evan's chiral auxiliary was applied to the construction of ring B together

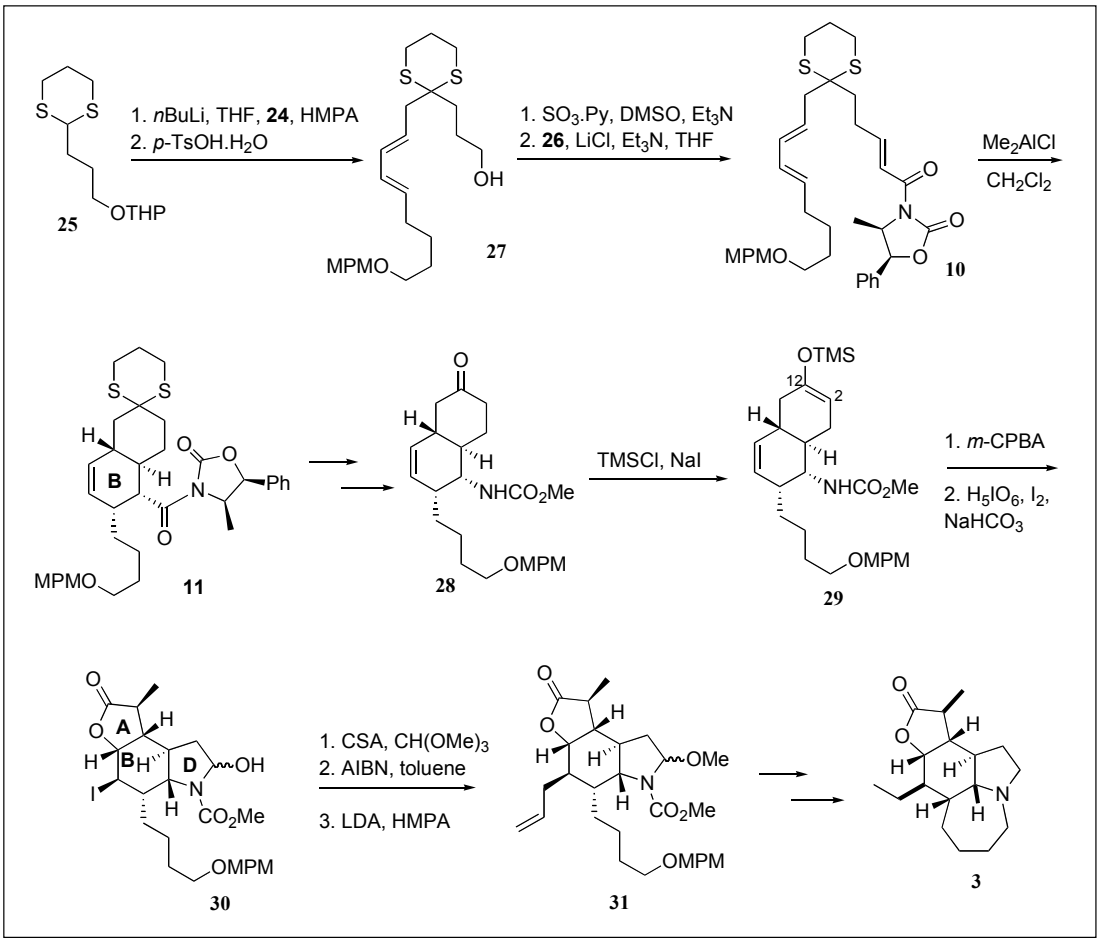
[7] Moromoto, Y.; Iwahashi, M.; Nishida, K.; Hayashi, Y.; Shirahama, H. *Angew. Chem. Int. Ed Engl.* **1996**, *35*, 904.

with the four stereogenic centers in **23**. The desired Diels-Alder precursor **10** was in turn assembled by convergent coupling of three fragments (dienyl chloride **24**, dithiane **25**, and chiral phosphonate **26**).



Scheme 3-5

First, an intramolecular asymmetric Diels-Alder reaction of the triene **10** prepared in a convergent fashion from three readily available components **24**, **25** and **26**. This was followed by an oxidative cleavage of C_2-C_{12} bond in trimethylsily enol ether **29** with *m*-chloroperbenzoic acid and orthoperiodic acid to afford an intermediary carboxylic acid derivative. Finally, an *in situ* iodolactonization stereoselectively formed the A, B and D ring system **30**. (Scheme 3-6)

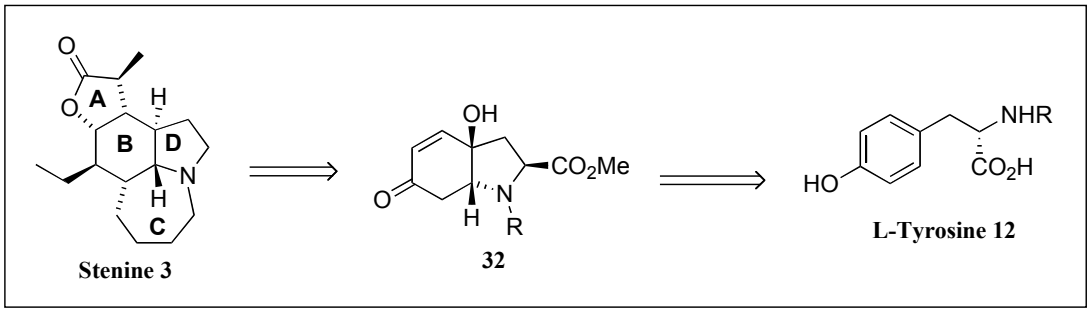


Scheme 3-6

3.2.2 Strategy 2: Functionalization of Readily Available Six-Membered Ring

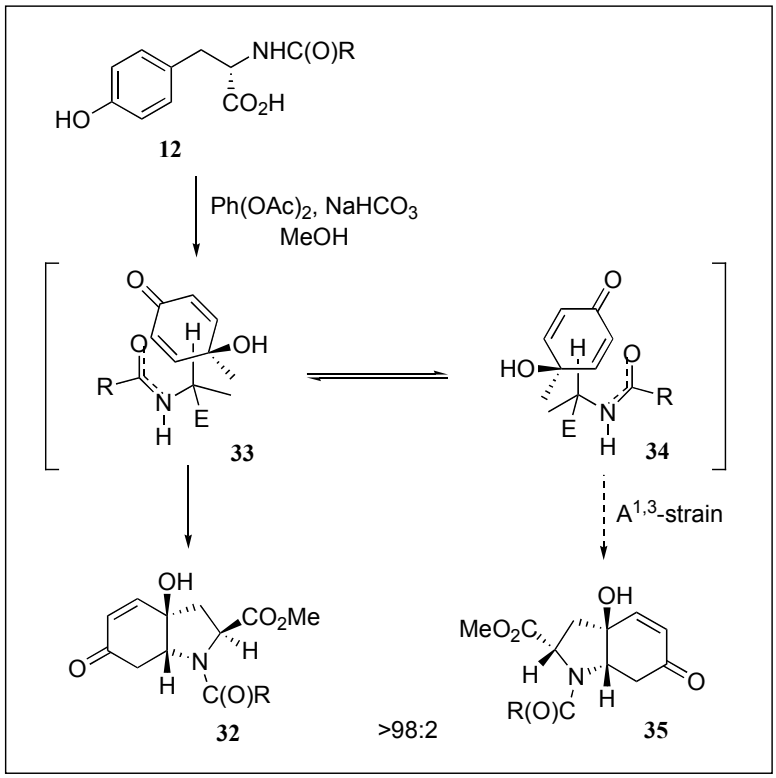
In 1995, Wipf and co-workers anticipated the first asymmetric synthesis of (-)-stenine starting from L-Tyrosine **(12)**.[8] They envisioned that the *trans*-fused perhydroindole present in **3** could be effectively transformed from the conversion of **32** through π-allylpalladium chemistry. (Scheme 3-7)

[8] Wipf, P.; Kim, Y.; Goldstein, D. M. *J. Am. Chem. Soc.* **1995**, *117*, 11106.



Scheme 3-7

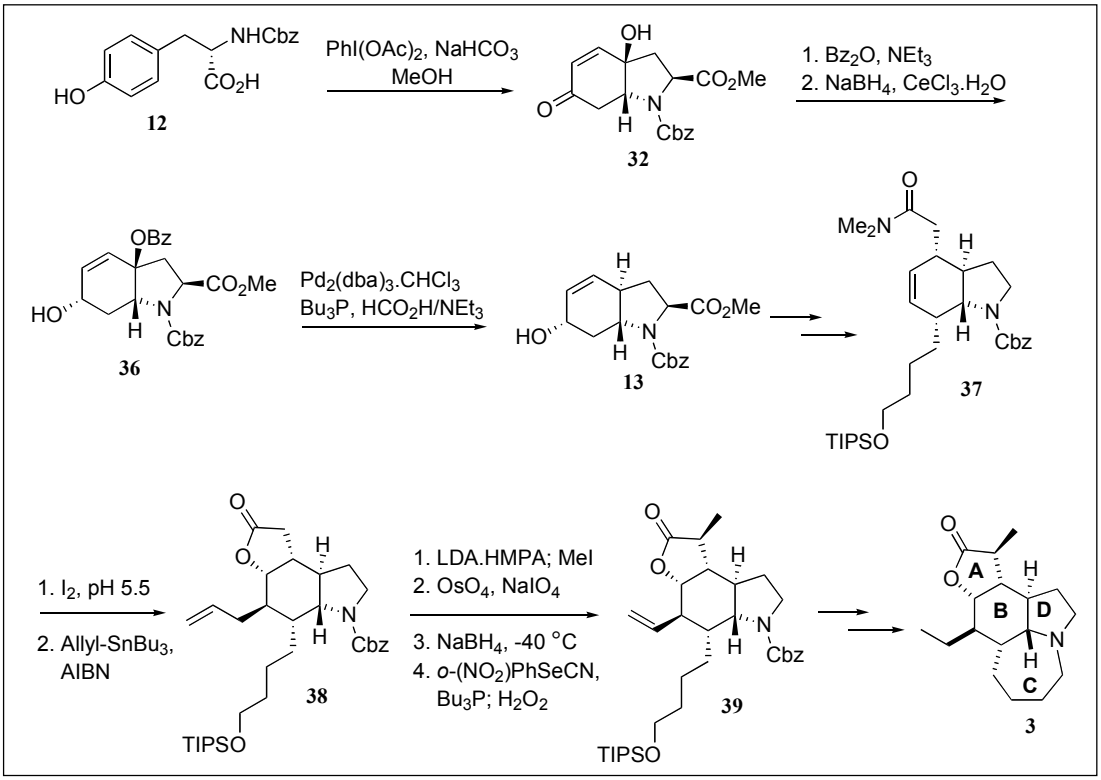
They carried out the synthesis of (-)-stenine (**3**) starting from L-tyrosine (**26**). The bicyclic **32** was constructed stereochemically pure in a single step from **26** (Scheme 3-9). The high selectivity of this diastereotopic end-group-differentiating cyclization is due to the destabilizing steric interactions in conformer **34**, owing to the $A^{1,3}$-strain between the amide oxygen and the methyl ester (*E*) substituent, and the facial interaction of the *trans*-amide and enone π-systems. (Scheme 3-8)



Scheme 3-8

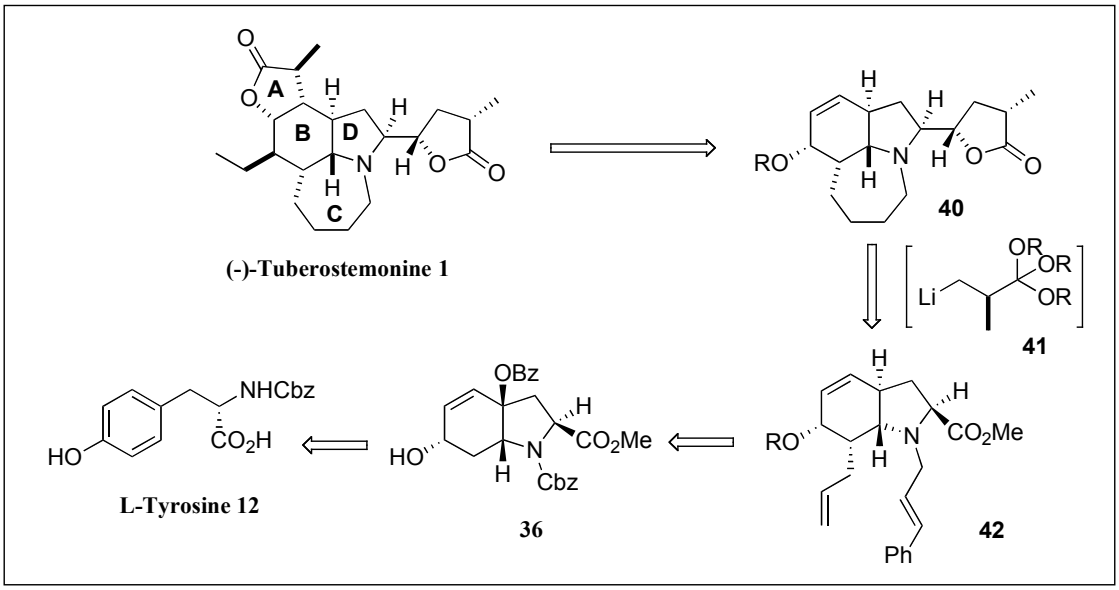
In their synthesis, π-allypalladium chemistry was applied in the conversion of the *cis*-hydroxyindole ring system **36** to the *trans*-fused perhydroindole **13** in which the optimum condition was achieved by using catalytic tris(dibenzylidene-acetone)-dipalladium (0) chloroform complex (2.5 mol%), tributylphosphine (10 mol%), and triethylammonium formate at 60 °C under strictly anaerobic conditions.

Intermediate **38** was obtained *via* Keck allylation in neat allyltributylstannane in 77% yield. Methylation of the lactone, and subsequent conversion of the allyl to a vinyl group by a Johnson-Lemieux oxidation, reduction, and Grieco-elimination sequence provided tricycle **39** in 54% yield. After a series of functional group manipulations, they completed the total synthesis of (-)-stenine (**3**) with an overall yield of 2% for the 25-step sequence starting with bicycle **36** (Scheme 3-9).



Scheme 3-9

Later in 2002, Wipf and co-workers reported the first total synthesis of tuberostemonine (**1**). The key synthetic sequence of their retrosynthetic analysis is a ring-closing metathesis reaction to form the azepane to **40** followed by the addition of a lithiated ortho ester **41** to introduce the right-side butyrolactone (Scheme 3-10). Bicycle **36**, which is obtained in three steps from Cbz-L-tyrosine as described in their stenine synthesis,[9] served as a scaffold for installation of nine of the ten stereogenic carbons of tuberostemonine, including the fused leftside butyrolactone which is obtained by a Claisen rearrangement and halolactonization.



Scheme 3-10

Their synthesis began from bicycle **36**, which is subjected to a series of transformations to obtain intermediate **42** (Scheme 3-11). It was followed by an azepine ring-closing metathesis by refluxing **42** in CH_2Cl_2 in the presence of 2-5 mol% of the ruthenium catalyst **44**. The resulting double bond in azepine **45** was

[9] (a) Wipf, P.; Kim, Y.; Goldstein, D. M. *J. Am. Chem. Soc.* **1995**, *117*, 11106-11112. (b) Wipf, P.; Methot, J. -L. *Org. Lett.* **2000**, *2*, 4213-4216. (c) Wipf, P.; Mareska, D. A. *Tetrahedron Lett.* **2000**, *41*, 4723-4727. (d) Wipf, P.; Li, W. *J. Org. Chem.* **1999**, *64*, 4576-4577.

removed in a three-step sequence to give tricycle **46** after transient protection of the enone double bond by conjugate addition-elimination of thiophenol. Ester **46** was obtained as a single diastereomer after Luche's reduction and TBDMS protection. The right-side butyrolactone was later introduced to afford the desired lactone **47** as a single diastereomer in 70% yield. This reaction accomplished by first isomerizing the allyl group followed by cross-metathesis propenylvinyl exchange in the presence of ruthenium catalyst. The pentacyclic *Stemona* alkaloid tuberostemonine was prepared in 24 steps with an overall yield of 1.4% from bicycle **36**.

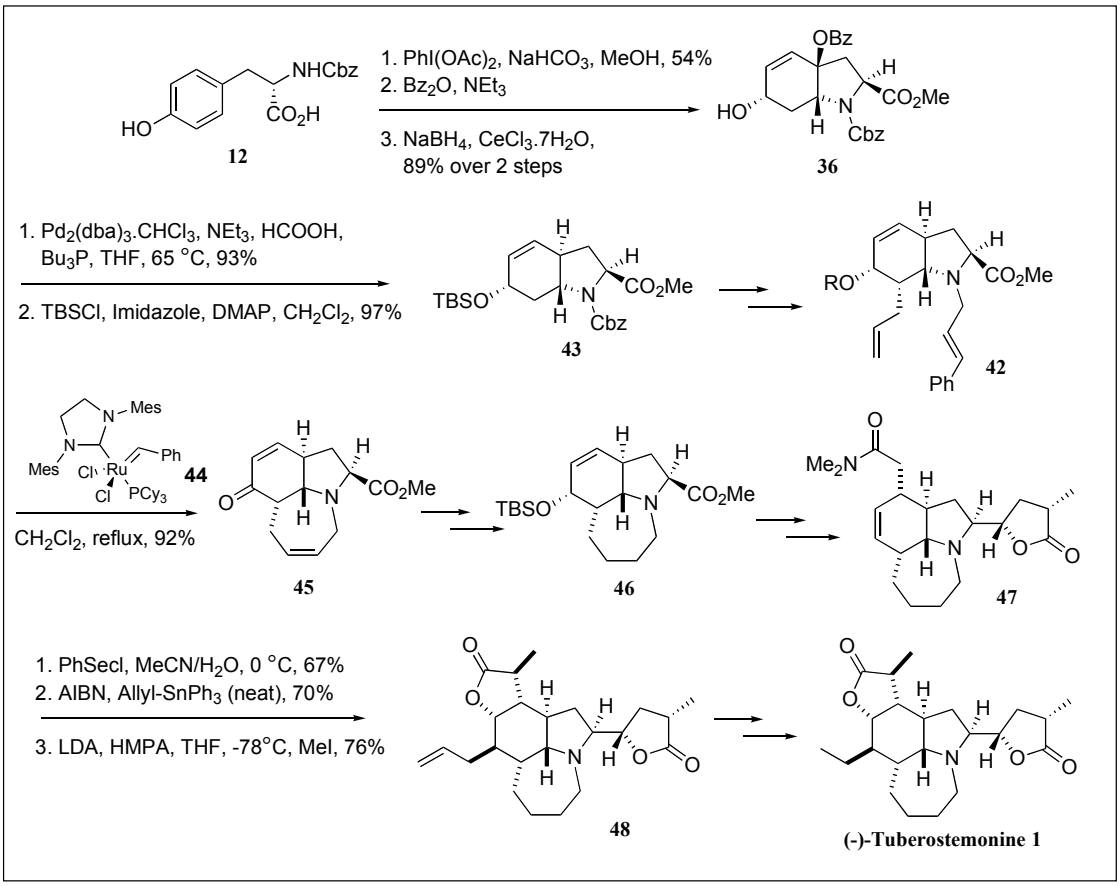
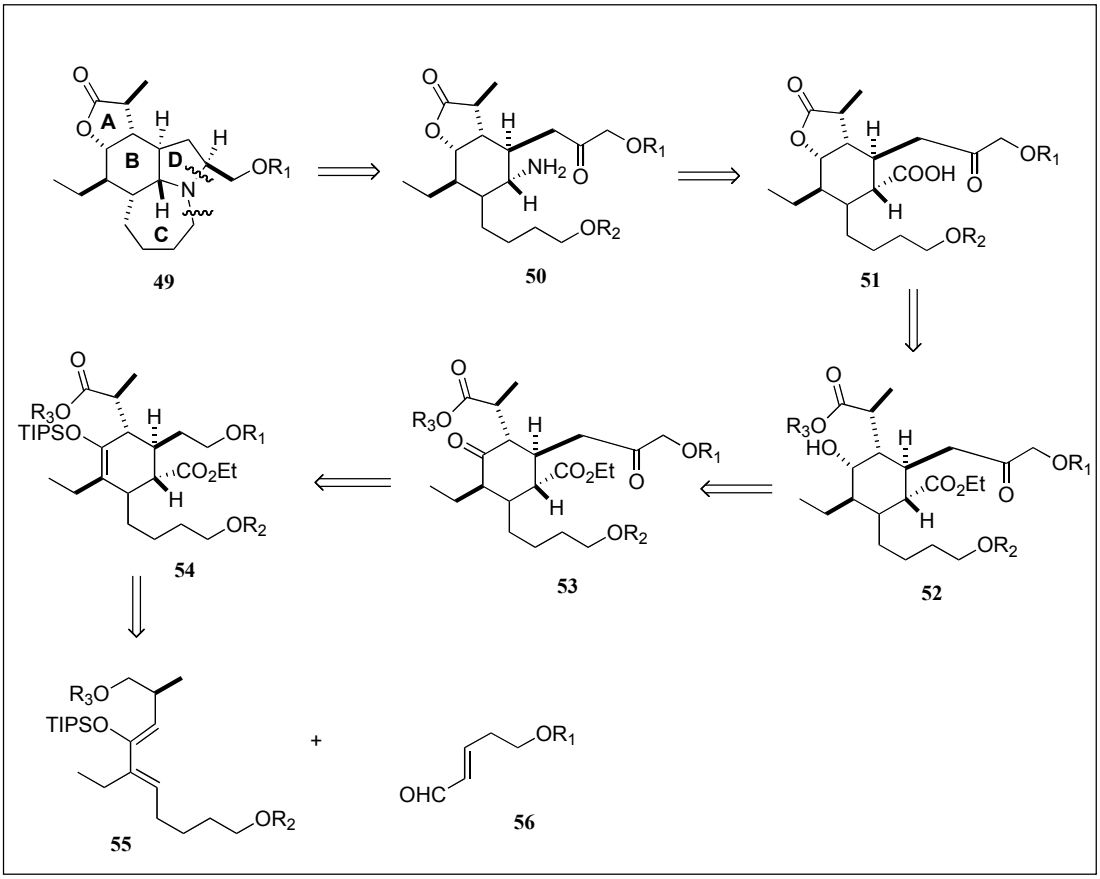


Figure 3-11

3.3 Our Synthetic Strategy



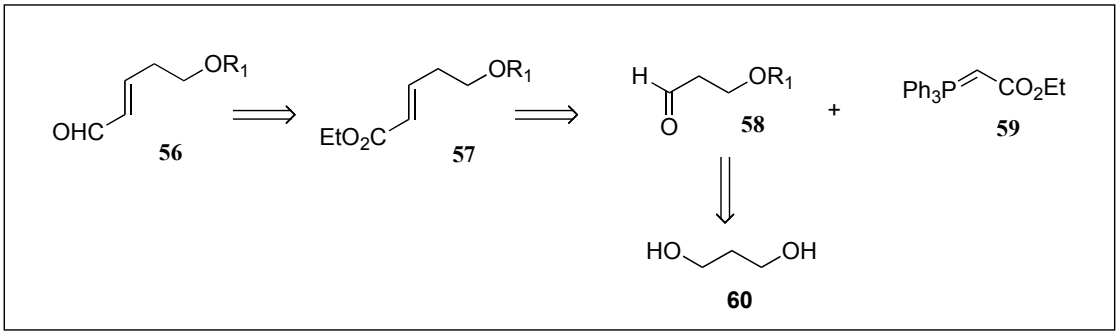
Scheme 3-12

The retrosynthetic approach to tuberostemonine is shown in Scheme 3-12. Our approach relies on an intermolecular Diels-Alder reaction to construct and control stereochemistries of the substituents around ring B. Indium-mediated allylation reaction was employed as the key step to synthesize the corresponding diene for the intermolecular Diels-Alder reaction.

From the retrosynthetic analysis (Scheme 3-12), tuberostemonine (**1**) was envisioned to arise from a six-membered B ring system **54** where rings C and D are formed from the extensions about ring B. Ring D was planned to be constructed *via*

reductive amination and later on ring C by a S_N2 reaction on the amino group. **50** was prepared through a Curtius rearrangement from **51**. It was anticipated that the A ring in lactone **51** would be prepared from a lactonization of **52** which in turn can be prepared from a stereoselective reduction of **53**. Cleavage of triisopropylsilyl protecting group on molecule **54** will furnish us with ketone **53**. Cycloadduct **54** could be formed *via* a Lewis acid-catalyzed intermolecular Diels-Alder reaction between diene **55** and dienophile **56**.

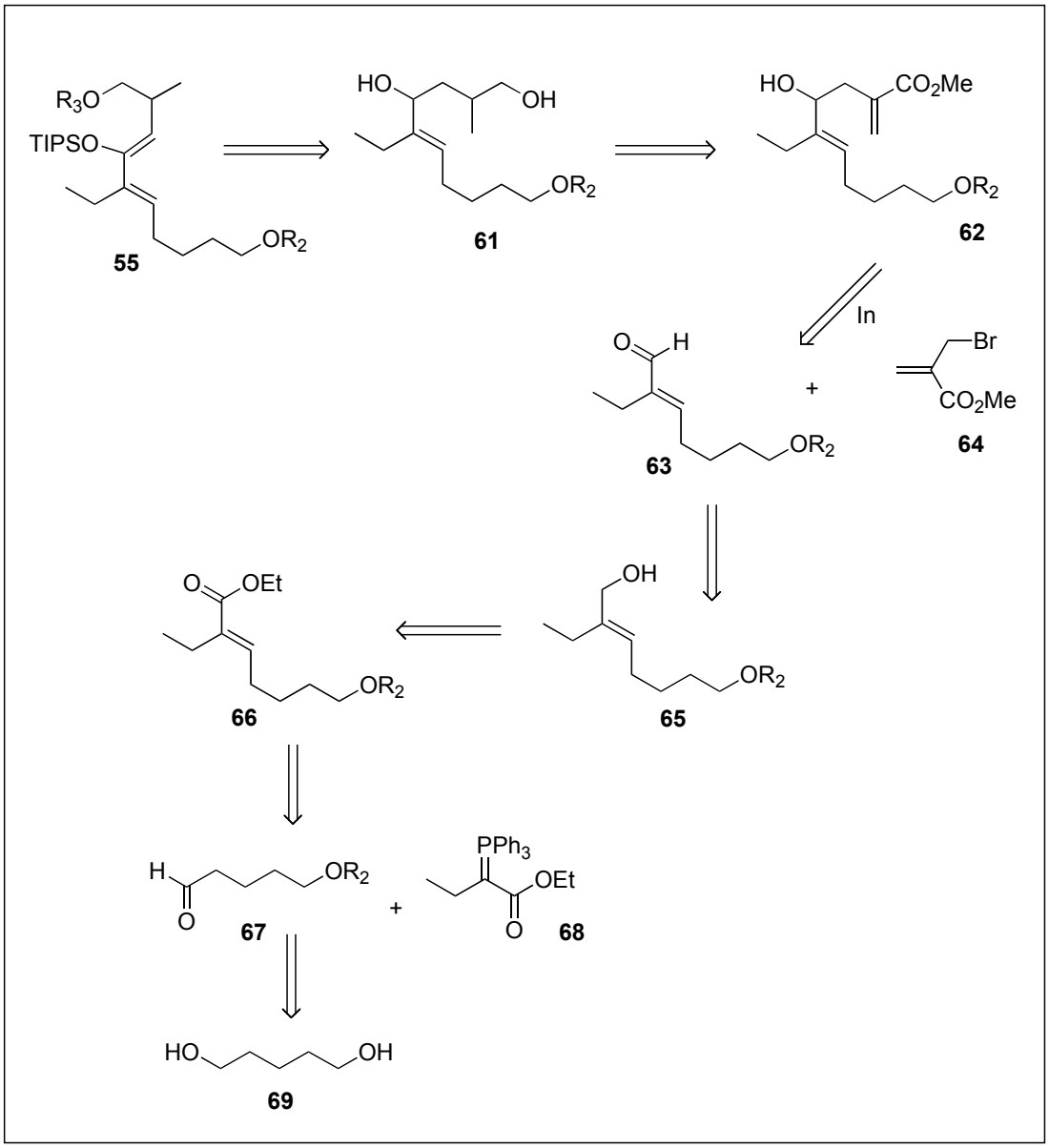
The α,β-unsaturated aldehyde **56** can be obtained from the Wittig reaction of the 1,3-propionaldehyde **58**, with stabilized ylide **59**, followed by a reduction-oxidation sequence of **57**. Aldehyde **58** in turn, can be obtained from commercially available 1,3-propanediol **60**. (Scheme 3-13)



Scheme 3-13

Synthesis of diene **55** can be achieved by applying the highly efficient indium-mediated allylation reaction (Scheme 3-14). The α,β-unsaturated aldehyde **63** was prepared by a reduction-oxidation sequence from the α,β-unsaturated ester **66** which can be synthesized from a Wittig reaction of aldehyde **67** and the stabilized ylide **68**

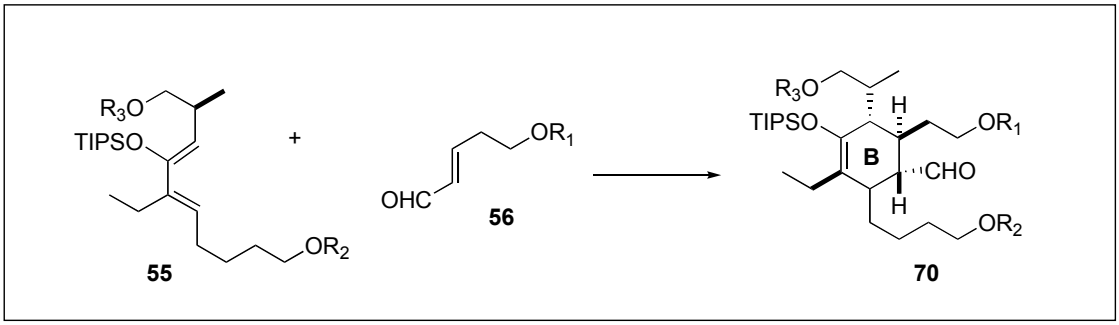
obtained from bromo ethylbutyrate. Aldehyde **67** in turn could be prepared from commercially available 1,5-pentanediol **69** (Scheme 3-14).



Scheme 3-14

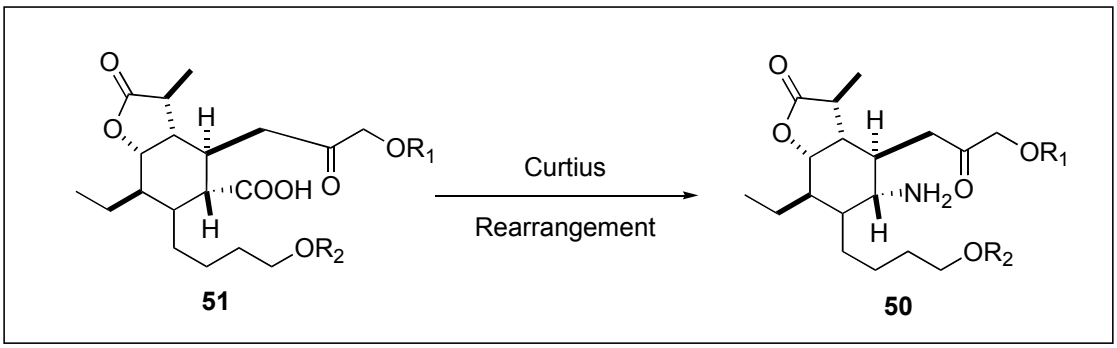
Our synthetic routes are as follows:

1. The core ring B may be derived from a Diels-Alder approach with the triisopropylsilyl group (TIPS) used as a protecting group for the diene and whose electron-donating properties would assist in the 1,4 direction of the intermolecular Diels-Alder reaction. In addition, the Diels-Alder reaction would proceed *via* the well-established *endo* transition state affording the product with the control of the four stereo centers in one step on the six-membered ring B (Scheme 3-15).



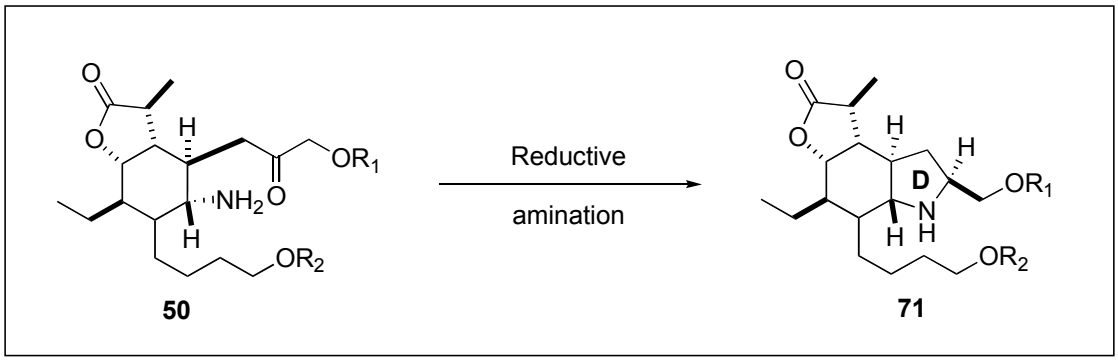
Scheme 3-15

2. A Curtius rearrangement would allow for the introduction of amino group with the retention of stereochemistry on ring B (Scheme 3-16).



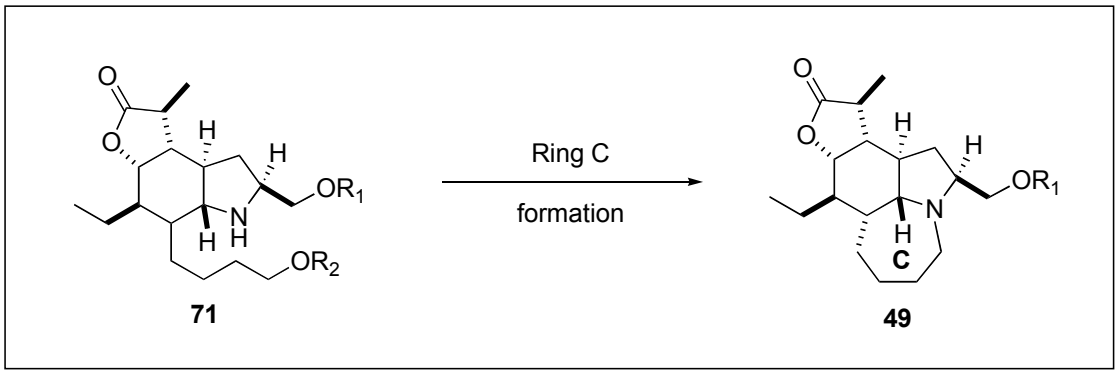
Scheme 3-16

3. Reductive amination or intermolecular S_N2 reaction to construct the pyrolidine ring D (Scheme 3-17).



Scheme 3-17

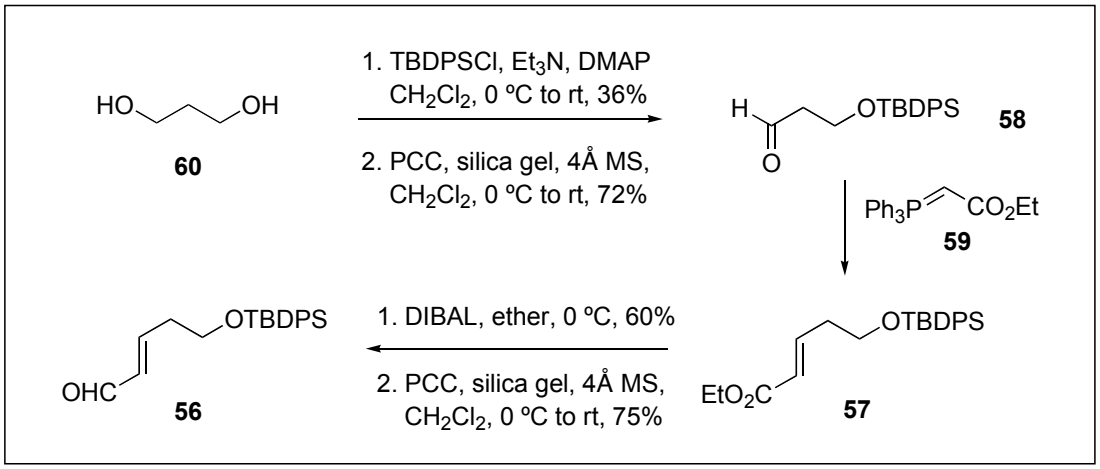
4. The construction of the seven-membered ring C after conversion of the protecting group R_2 to a tosylate group followed by a S_N2 reaction on the amino group to afford ring C (Scheme 3-18).



Scheme 3-18

3.4 Results and Discussions

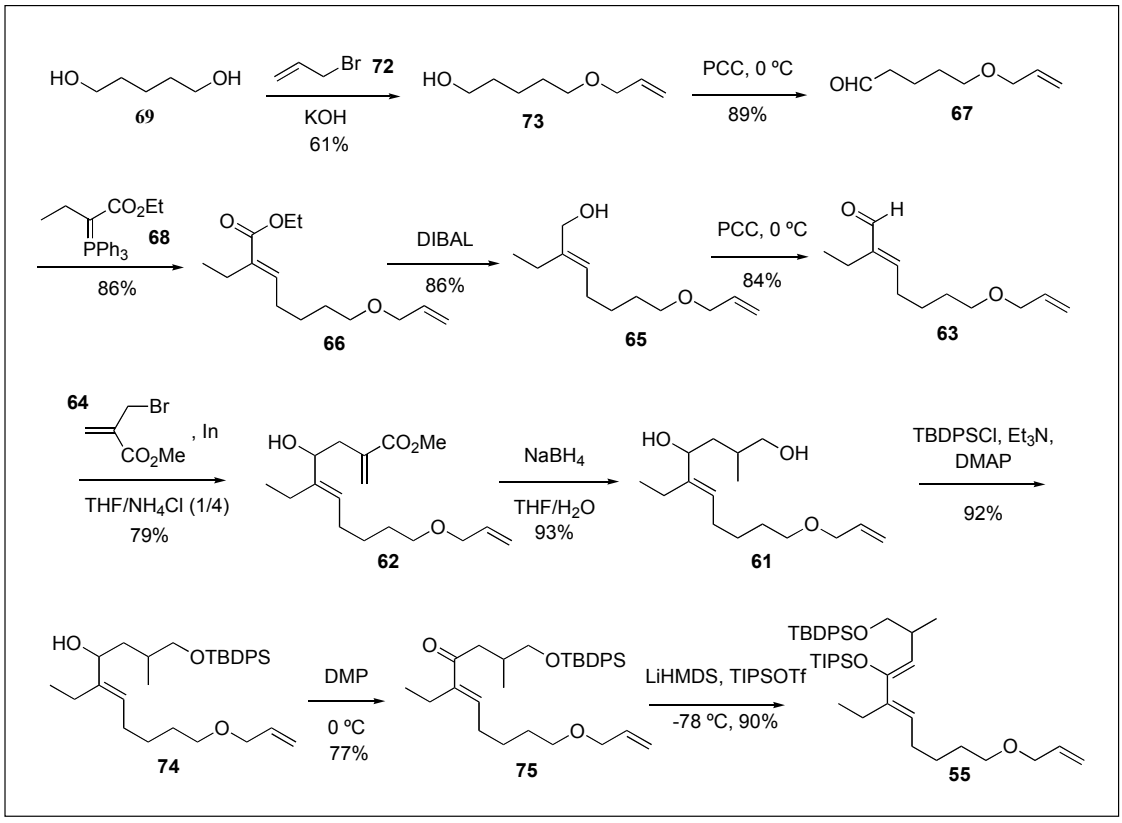
The dienophile **56** was available in 5 steps from commercially available 1,3-propanediol **60** (Scheme 3-19). Protection of 1,3-propanediol **60** with TBDPSCl, followed by PCC oxidation afforded aldehyde **58** in 26% yield (2 steps). Ester 57 was constructed *via* Wittig reaction of aldehyde **58** and stabilized ylide **59**. After an oxidation-reduction sequence, the desired dienophile **56** was obtained in 45% yield (2 steps).



Scheme 3-19

Diene **55** was synthesized from commercially available 1,5-pentanediol (**69**) as shown in Scheme 3-20. A selective protection on 1,5-pentanediol (**69**) with potassium hydroxide and allyl bromide (**72**) afforded the monoprotected alcohol **73** in 61% yield. Allyl bromide (**72**) was used as the protecting group as allylic ethers are known to be stable in both moderately acidic and basic conditions. Furthermore, the allyl group can be easily removed by refluxing with cerium (III) chloride and sodium iodide in acetonitrile with high chemoselectivity without strongly acidic or basic conditions.

Oxidation of alcohol **73** using pyridinium chlorochromate (PCC) gave aldehyde **67** in 69% yield. Wittig reaction was carried out between aldehyde **67** and a pre-stabilized ylide **68** to give the α,β-unsaturated ester **66** in 86% yield. The ester **66** was then reduced to the corresponding alcohol **65** using diisobutylaluminium hydride (DIBAL) in 87% yield. Oxidation of alcohol **65** with PCC furnished the desired aldehyde **63** in 84% yield.



Scheme 3-20

With aldehyde **63** in hand, we continued to embark on the synthesis of diene **55** *via* an indium-mediated allylation reaction with methyl 2-(bromomethyl) acrylate (**64**) in aqueous media as the key step (Scheme 3-18). In the previous synthetic study towards the total synthesis of tuberostemonine (**1**), allylation reaction in THF/*sat.*

NH_4Cl (1/4) was shown to give the best result. The product was obtained as racemic hydroxyl ester **62** in good yield (79%).

Treatment of alcohol **62** with $NaBH_4$ (excess) gave the diol **61** in 93% yield. Selective protection of the primary alcohol of **61** with *t*-butyldiphenylsilylchloride (TBDPSCl) gave alcohol **74** in 92% yield. Dess-Martin periodinane oxidation of alcohol **74** gave ketone **75** in 77% yield.

Finally the synthesis of diene **55** was achieved through the formation of (Z)-enolate from ketone **75** using lithium bis(trimethylsilyl)amide (LiHMDS) and triisopropylsilyl triflate (TIPSOTf) in 90% yield. The stereochemistry of diene **55** was confirmed using NOESY spectroscopy (Figure 3-1).

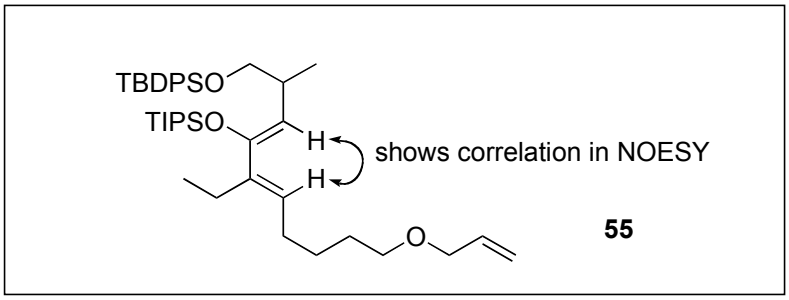
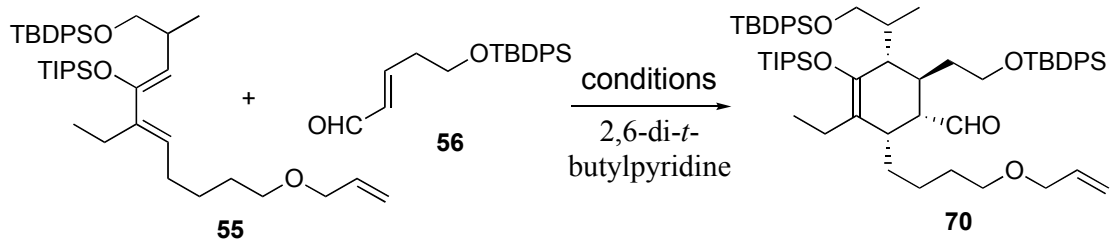


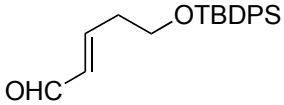
Figure 3-1

After successfully obtaining diene **55**, we proceeded to explore the Diels-Alder reaction with the dienophile **56**. Using the same reaction condition as described in Chapter 2, the Diels-Alder reaction was carried out with dienophile **56** and dienes **55** with boron trifluoride dietherate ($BF_3.OEt_2$) as the Lewis acid in CH_2Cl_2. In order to prevent the TIPS protecting group from being cleaved during the reaction, proton scavengers such as 2,6-di-*t*-butylpyridine was added during the reaction. The reaction

was first started at -78 °C and warmed up slowly. The progress of the reaction was monitored using TLC. No desired product was detected from the crude mixture and diene **55** decomposed in most cases. Several other conditions had also been tried and the results are summarized in Table 3-1.

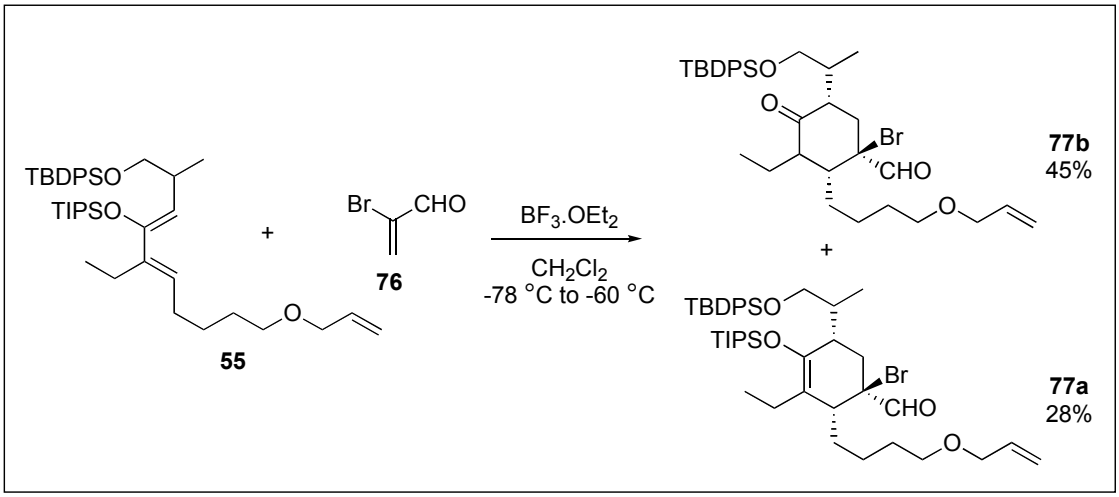
Table 3-1



Entry	Dienophile	Lewis Acid	Conditions	Results
1		$BF_3.OEt_2$ 0.5 equiv	-78 °C to rt 8d	Diene decomposed
2		$In(OTf)_3$ 0.5 equiv	-78 °C to rt 8d	
3		$TiCl_4$ 0.5 equiv	-78 °C to rt 8d	
4		$SnCl_4$ 0.5 equiv	-78 °C to -20 ºC 5d	
5		$Sm(OTf)_3$ 0.5 equiv	-78 °C to rt 8d	
6		$AlCl_3$ 0.5 equiv	-78 °C to rt 8d	

The reaction was then attempted with a more activated dienophile, bromoacrolein **76**. When bromoacrolein **76** was reacted with diene **55**, the cycloadducts **77a** and **77b** were obtained in 28% and 45% yields respectively (Scheme 3-21). The regiochemistry and relative stereochemistry of **77** was

determined by NOESY spectroscopy. It showed that the reaction had proceeded by the *endo* transition state to give the product **77** (Figure 3-2).



Scheme 3-21

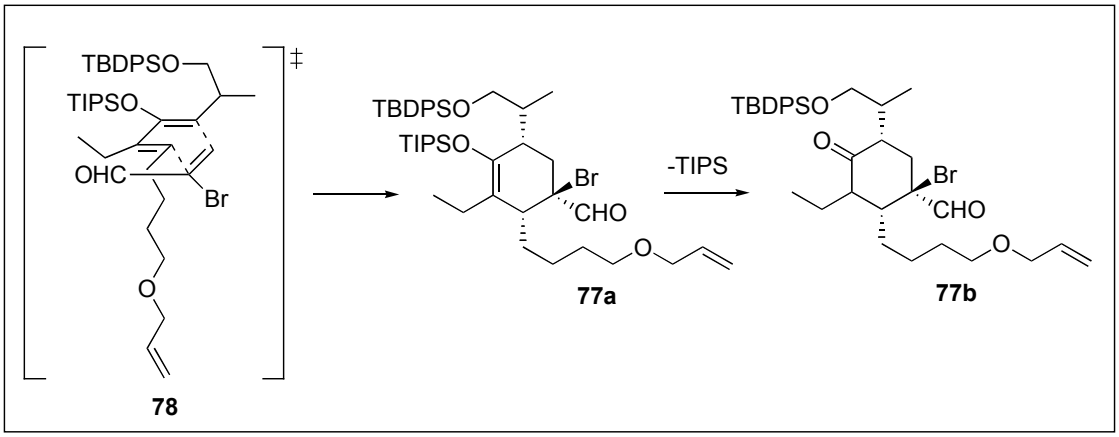
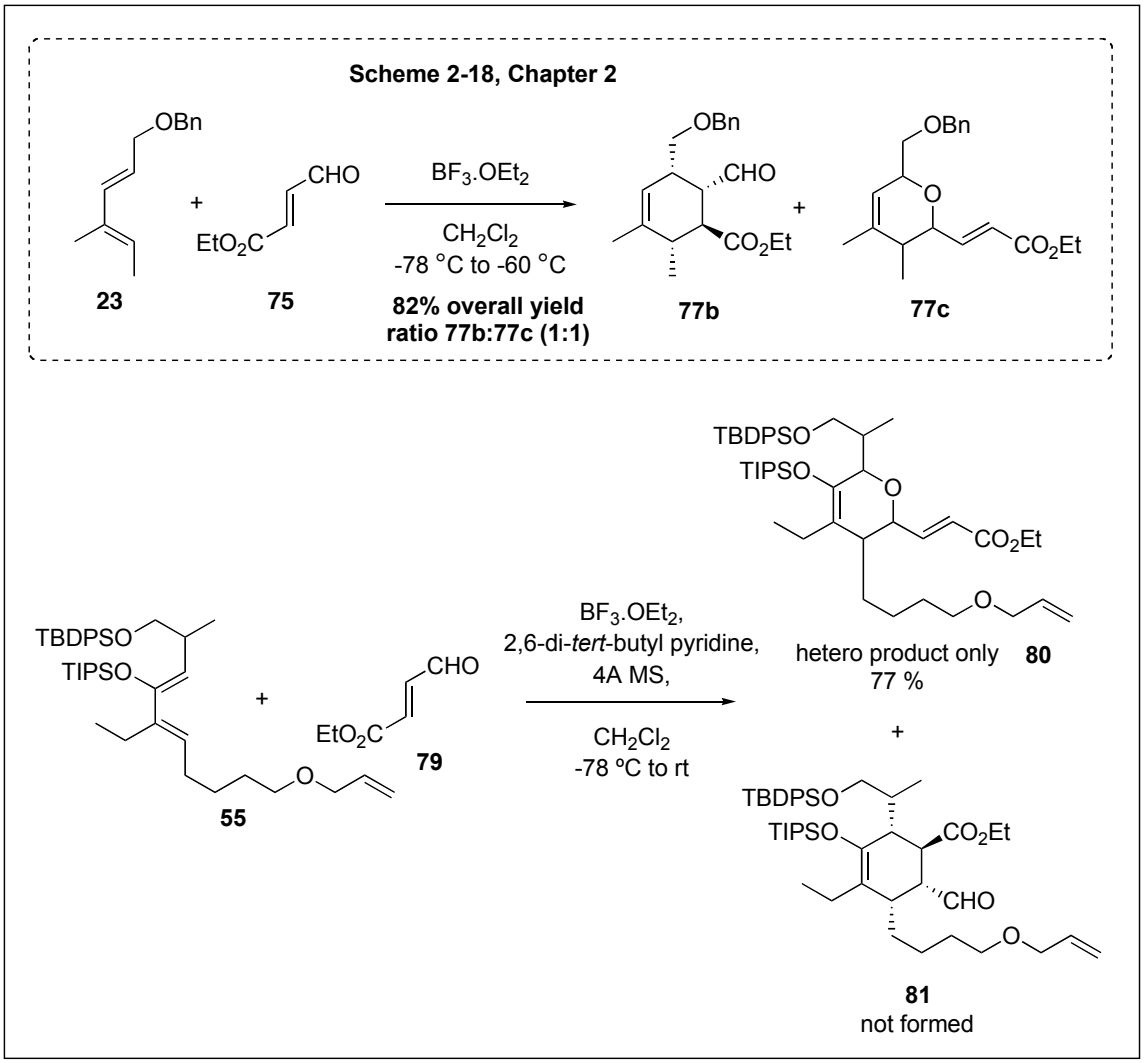


Figure 3-2

From the study done in chapter 2, we have successfully synthesized the cycloadduct **77b** using $BF_3.OEt_2$ as the Lewis acid (Scheme 2-18, Chapter 2). Thus, we explored the possibility of synthesizing aldehyde-ester **81** using our established system. However, only hetero-Diels-Alder product **80** was obtained in 77% yield from the reaction. (Scheme 3-22)



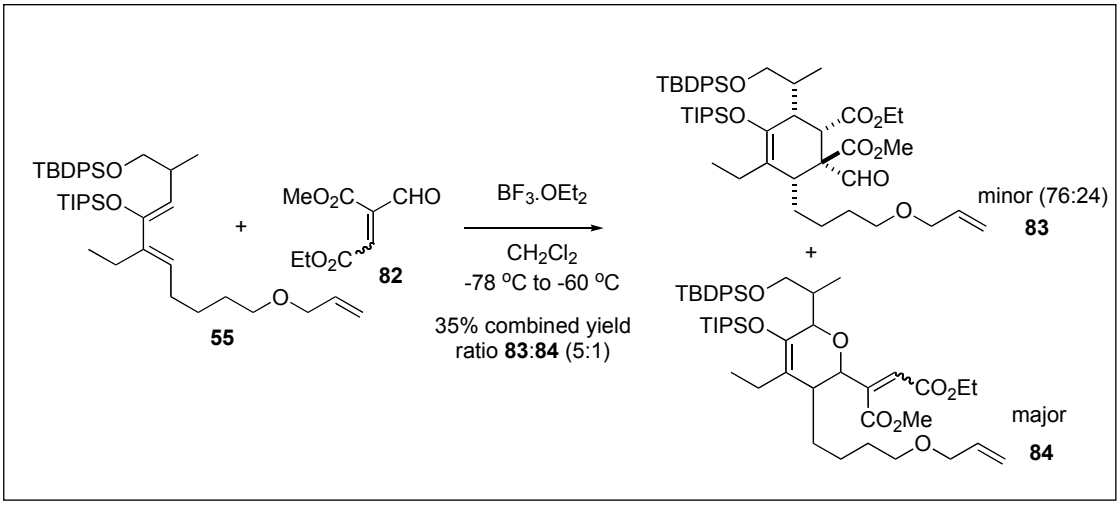
Scheme 3-22

Since $BF_3.OEt_2$ in CH_2Cl_2 does not yield any desired cycloadduct, other reaction conditions were studied. Non-polar solvents such as toluene was used in hope that it could suppress the hetero-Diels-Alder reaction. Again, only the hetero-Diels-Alder product was obtained with comparable yields in all cases (Table 3-2).

Table 3-2

Entry	Lewis acid	Solvent	Conditions	Product
1	$BF_3.OEt_2$	CH_2Cl_2	-78 °C to -60 °C for overnight	Hetero product only
2	$BF_3.OEt_2$	Toluene	-78 °C to -60 °C for overnight	Hetero product only
3	$TiCl_4$	CH_2Cl_2	-78 °C to -60 °C for overnight	Hetero product only
4	$TiCl_4$	Toluene	-78 °C to -60 °C for overnight	Hetero product only

Apart from dienophile **79**, we also explored dienophile **82** using the same reaction condition. The reaction was performed in CH_2Cl_2 with $BF_3.OEt_2$ as catalyst, and cycloadduct **83** was detected in the reaction mixture. Same as previous results, two competing reaction occurred. The hetero-cycloaddition yielded the major product **84** (Scheme 3-23). The stereochemistry of adduct **83** was suggested in Figure 3-3 based on the NOESY spectroscopy. This suggestion follows the conventional Diels-Alder reaction stereochemical outcome, *endo*-preference to give the product **83**. This is also consistent with our previous studies described in Chapter 2.



Scheme 3-23

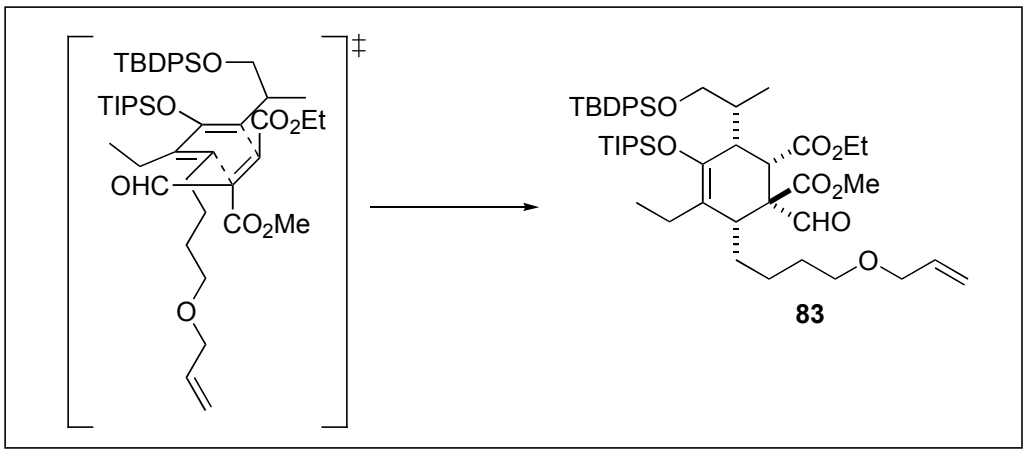
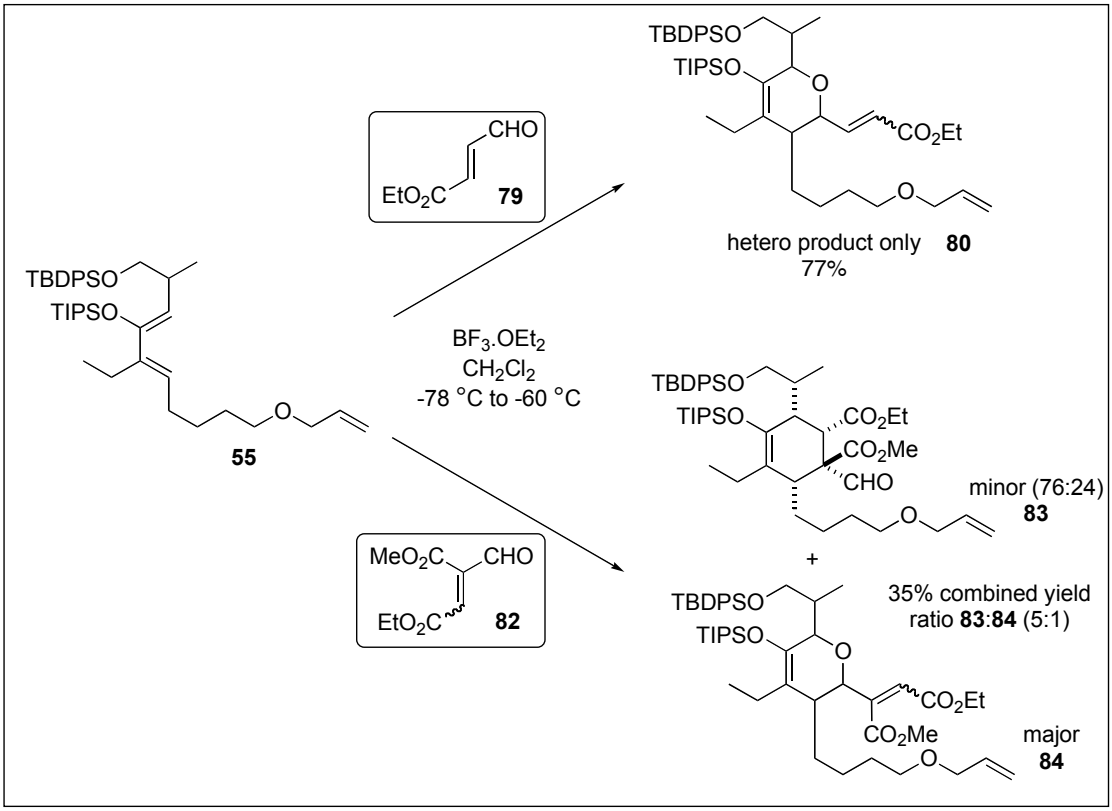


Figure 3-3

3.5 Conclusion

In conclusion, we have successfully synthesized multifunctionalized diene **55** in 10 steps from commercially available 1,5-pentanediol in 16% overall yield. Unfortunately, no desired products were obtained in the reaction between the proposed diene **55** and dienophile **56**. A series of Lewis acids ($BF_3.OEt_2$, $SnCl_4$, $TiCl_4$, $AlCl_3$, $In(OTf)_3$, $Sm(OTf)_3$, $InCl_3$) were tried. However, no desired cycloadduct was obtained. One possible explanation is that the multifunctionalized open chain diene was too bulky which hindered the cycloaddition process. Besides, the β-substituted on the dienophile **56** reduces the reactivity of the dienophile.

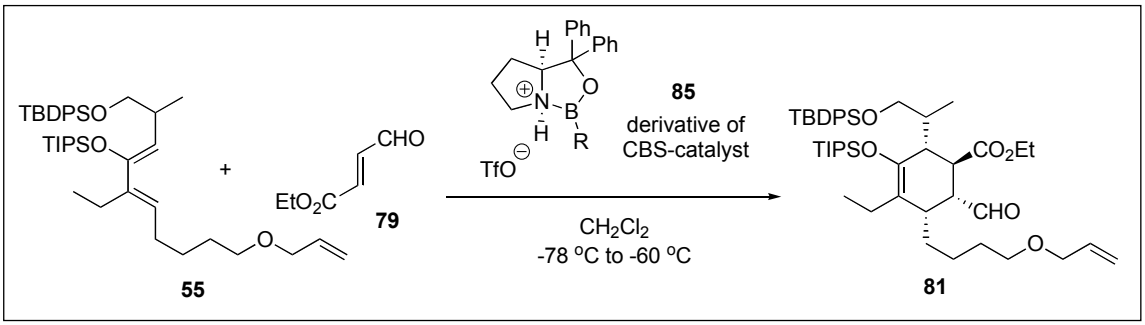


Scheme 3-24

When we perform the Diels-Alder reaction with the more reactive dienophile such as aldehyde ester **79**, only the hetero-Diels-Alder product was obtained from the reaction mixture. Condition optimizations were carried out using different Lewis acid or less polar solvent such as toluene. Likewise, only hetero product was obtained. Using dienophile **82**, we manage to synthesis the cycloadduct **83**. Even though cycloadduct **83** is not the desired product for the total synthesis of tuberostemonine, this finding is useful in other synthesis which require more complicated dienes such as diene **55**. Besides, intermolecular Diels-Alder reaction with multifunctionalized diene and dienophile using Lewis acid catalyst to synthesize the six membered cyclohexane ring has not been reported.

3.6 Future Works

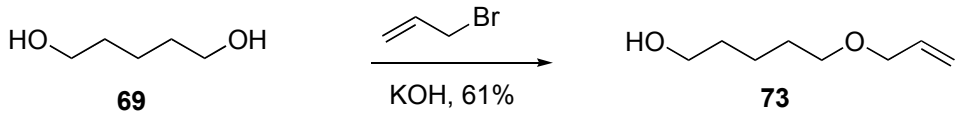
The exploration of more efficient Lewis acid is needed. Due to time constraint, exploration on chiral Lewis acids has not been studied. A versatile oxazoborolidine chiral ligand such as derivative of CBS-catalyst (Corey-Bakshi-Shibata-catalyst, **85**) might be a good catalyst for this reaction system (scheme 3-24).



Scheme 3-24

3.7 Experimental

5-Allyloxypentan-1-ol (73)



To commercially available 1,5-pentanediol **69** (60.0 mL, 0.58 mol) in 100 mL THF was added potassium hydroxide (32.2 g, 0.58 mol) and catalytic amount of phase-transfer catalyst, *t*-butyl ammonium bromide, pre-dissolved in water (60 mL), dropwise at 0 °C. Allyl bromide (44.6 mL, 0.52 mol) dissolved in CH_2Cl_2 was then added at 0 °C and stirred for 3 days at room temperature. The product was extracted with CH_2Cl_2 (3 x 100 mL), washed with brine (2 x 100 mL) and dried over anhydrous $MgSO_4$. The solvent was removed *in vacuo*. Purification *via* column chromatography with 20% ethyl acetate in hexane gave the product **73** in 61% (41.8 g) yield.

R_f = 0.125 (Hexane:EtOAc, 4:1);

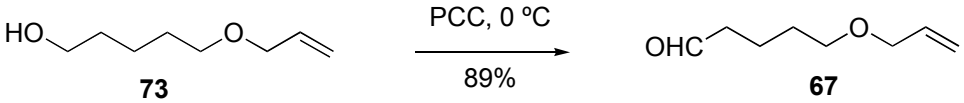
^{1}H NMR (300 MHz, $CDCl_3$): δ 1.34-1.41 (2H, m, -$CH_2CH_2C\mathbf{H}_2CH_2CH_2$), 1.48-1.61 (4H, m, -$CH_2CH_2CH_2C\mathbf{H}_2CH_2$), 2.50 (1H, brs, O**H**), 3.39 (2H, t, *J* = 6.27 Hz, -$C\mathbf{H}_2OH$), 3.56 (2H, t, *J* = 6.27 Hz, -$C\mathbf{H}_2$O-allyl), 3.91 (2H, d, *J* = 5.57 Hz, -$OC\mathbf{H}_2CH{=}CH_2$), 5.10 (1H, dd, *J* = 10.5, 1.05 Hz, -CH=C$\mathbf{H}_2$), 5.18 (1H, dd, *J* = 17.20, 1.39 Hz, -CH=C$\mathbf{H}_2$), 5.79-5.92 (1H, m, -C**H**=CH_2) ppm;

^{13}C NMR (75 MHz, $CDCl_3$): δ 22.3 (-$\mathbf{C}H_2CH_2CH_2OH$), 29.3 (-$\mathbf{C}H_2CH_2OCH_2$-), 32.3 (-$\mathbf{C}H_2CH_2OH$), 62.4 (-$CH_2\mathbf{C}H_2OH$), 70.2 (-$\mathbf{C}H_2$O-ally), 71.7 (-$O\mathbf{C}H_2CH{=}CH_2$), 116.8 (-CH=$\mathbf{C}H_2$), 134.8 (-$\mathbf{C}H{=}CH_2$) ppm;

FTIR (neat, cm^{-1}): 3391, 2938, 2864, 1458, 1421;

HRMS (EI [M]$^+$): *m/e* calculated for $[C_8H_{16}O_2]^+$ = 114.1150, found = 114.1135.

5-Allyloxypentanal (67)



73 **67**

To 4Å molecular sieve (40 g) and silica gel (40 g), both pre-dried in the oven and cooled under vacuum, was added pyridium chlorochromate (244 g, 1.05 mol) and dry CH_2Cl_2 (450 mL). The suspension was stirred at 0 °C for 10 minutes prior to addition of **73** (41.8 g, 0.31 mol) pre-diluted with dry CH_2Cl_2 (50 mL) drop-wise. The mixture was allowed to stir at 0 °C for 6 hours prior to work-up. The reaction mixture was filtered through a sintered glass funnel packed with silica gel and washed with copious CH_2Cl_2. The filtrate was dried over anhydrous $MgSO_4$. The solvent was removed *in vacuo*. Product **67** was obtained in 89% (39.2 g) yield.

$\mathbf{R_f}$ = 0.25 (Hexane:EtOAc, 4:1);

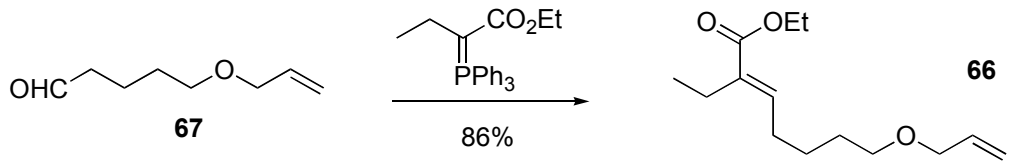
^{1}H NMR (300 MHz, $CDCl_3$): δ 1.59-1.77 (4H, m, -CH_2C**H**$_2$C**H**$_2$$CH_2$), 2.46 (2H, td, *J* = 6.97, 1.05 Hz, -C**H**$_2$CHO), 3.43 (2H, t, *J* = 6.27 Hz, -C**H**$_2$O-allyl), 3.95 (2H, d, *J* = 5.57 Hz, -OC**H**$_2$CH=CH_2), 5.16 (1H, dd, *J* = 10.50, 0.70 Hz, -CH=C**H**$_2$), 5.26 (1H, dd, *J* = 17.2, 1.39 Hz, -CH=C**H**$_2$), 5.82-5.96 (1H, m, -C**H**=CH_2), 9.76 (1H, s, -C**H**O) ppm;

^{13}C NMR (75 MHz, $CDCl_3$): δ 19.0 (-**C**H_2CH_2CHO), 29.1 (-**C**$H_2CH_2CH_2CHO$), 43.6 (-**C**H_2CHO), 69.7 (-**C**H_2O-ally), 71.8 (-O**C**H_2CH=CH_2), 116.9 (-CH=**C**H_2), 134.9 (-**C**H=CH_2), 202.6 (-**C**HO) ppm;

FTIR (neat, cm^{-1}): 2942, 2865, 2788, 1735, 1457, 1422;

HRMS (EI [M]$^+$): *m/e* calculated for $[C_8H_{14}O_2]^+$ = 142.0994, found = 142.0949.

7-Allyloxy-2-ethylhept-2-enoic acid ethyl ester (66)



To pre-form stabilized ylide (7.58 g, 0.17 mol) and anhydrous sodium carbonate (20.0 g) in dry THF (100 mL) was added **67** (15.7 g, 0.11 mol), pre-diluted in dry THF (30 mL). The resulting mixture was refluxed at 80 °C for 24 hours. THF was removed *in vacuo*. Purification *via* column chromatography with 3% ethyl acetate in hexane gave the product **66** in 86% (22.8 g) yield. Only the *E*-isomer was obtained.

$\mathbf{R}_f$ = 0.55 (Hexane:EtOAc, 4:1);

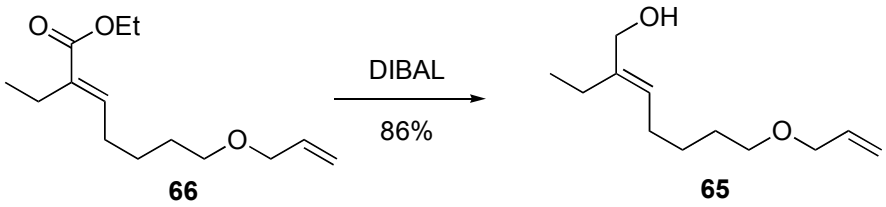
^{1}H NMR (300 MHz, $CDCl_3$): δ 0.95 (3H, t, *J* = 7.63 Hz, C**H**$_3$CH$_2$C=CH-), 1.23 (3H, t, *J* = 7.23 Hz, -OCH$_2$C**H**$_3$), 1.42-1.62 (4H, m, -C=CHCH$_2$C**H**$_2$C**H**$_2$), 2.15 (2H, q, *J* = 7.23 Hz, -C=CHC**H**$_2$), 2.25 (2H, q, *J* = 7.63 Hz, CH$_3$C**H**$_2$CH=CH$_2$), 3.38 (2H, t, *J* = 6.42 Hz, -CH$_2$C**H**$_2$O-), 3.90 (2H, d, *J* = 5.64 Hz, -OC**H**$_2$CH=CH$_2$), 4.13 (2H, q, *J* = 7.23 Hz, -OC**H**$_2$CH$_3$), 5.10 (1H, dd, *J* = 10.20, 1.61 Hz, -CH=C**H**$_2$), 5.20 (1H, dd, *J* = 17.30, 1.61 Hz, -CH=C**H**$_2$), 5.79-5.91 (1H, m, -C**H**=CH$_2$), 6.65 (1H, t, *J* = 7.63 Hz, -C=C**H**CH$_2$) ppm;

^{13}C NMR (75 MHz, $CDCl_3$): δ 13.8 (-CH$_2$**C**H$_3$), 14.1 (-OCH$_2$**C**H$_3$), 19.9 (-**C**H$_2$CH$_3$), 25.4 (-C=CH**C**H$_2$-), 28.0 (-C=CHCH$_2$**C**H$_2$-), 29.3 (-**C**H$_2$CH$_2$O-ally), 60.1 (-O**C**H$_2$CH$_3$), 69.9 (-**C**H$_2$O-ally), 71.7 (-O**C**H$_2$CH=CH$_2$), 116.6 (-CH=**C**H$_2$), 134.1 (-**C**=CHCH$_2$-), 134.8 (-**C**H=CH$_2$), 141.4 (-C=**C**HCH$_2$-), 167.7 (-**C**=O) ppm;

FTIR (neat, cm^{-1}): 2933, 2862, 1708, 1458;

HRMS (EI [M]$^+$): *m/e* calculated for $[C_{14}H_{24}O_3]^+$ = 240.1725, found = 240.1755

7-Allyloxy-2-ethylhept-2-ene-1-ol (65)



66 **65**

To **66** (21.7 g, 0.09 mol) in dry CH_2Cl_2 (100 mL) was added diisobutylammonium hydride (45.4 mL, 0.23 mol) dropwise at 0 °C. The reaction was allowed to stir for 2 hours prior to work-up. Saturated Na_2SO_4 was added at 0 °C to quench the reaction. The mixture was passed through a sintered glass funnel and washed with CH_2Cl_2. The filtrate was dried over anhydrous $MgSO_4$. The solvent was removed *in vacuo* to give the product **65** in 86% (15.3 g) yield.

$\mathbf{R_f}$ = 0.52 (Hexane:EtOAc, 4:1);

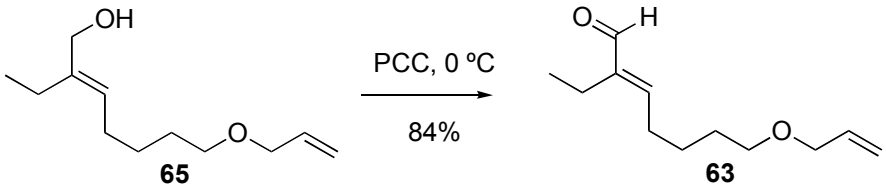
^{1}H NMR (300 MHz, $CDCl_3$): δ 0.98 (3H, t, *J* = 7.63 Hz, C**H**$_3$CH$_2$-), 1.24 (1H, brs, O**H**), 1.36-1.46 (2H, m, -C=CHCH$_2$C**H**$_2$-), 1.54-1.64 (2H, m, -C**H**$_2$CH$_2$O CH$_2$-), 2.01-2.12 (4H, m, -C=CHC**H**$_2$-, CH$_3$C**H**$_2$-), 3.41 (2H, t, *J* = 6.82 Hz, -C**H**$_2$O-allyl), 3.94 (2H, d, *J* = 5.62 Hz, -OC**H**$_2$CH=CH$_2$-), 4.01 (2H, s, -C**H**$_2$OH), 5.15 (1H, dd, *J* = 10.40, 1.61 Hz, -CH=C**H**$_2$), 5.35 (1H, t, *J* = 7.23 Hz, -C=C**H**CH$_2$), 5.82-5.96 (1H, m, -C**H**=CH$_2$) ppm;

^{13}C NMR (75 MHz, $CDCl_3$): δ 13.1 (-CH$_2$**C**H$_3$), 20.9 (-**C**H$_2$CH$_3$), 26.2 (-C=CHCH$_2$**C**H$_2$-), 26.9 (-C=CH**C**H$_2$CH$_2$-), 29.3 (-**C**H$_2$CH$_2$O-ally), 66.7 (-**C**H$_2$OH), 70.2 (-**C**H$_2$O-ally), 71.7 (-O**C**H$_2$CH=CH$_2$), 116.6 (-CH=**C**H$_2$), 126.0 (-C=**C**HCH$_2$-), 134.9 (-**C**H=CH$_2$), 140.8 (-**C**=CHCH$_2$-) ppm;

FTIR (neat, cm^{-1}): 3386, 2937, 2860, 1458, 1430;

HRMS (EI [M]$^+$): *m/e* calculated for $[C_{12}H_{22}O_2]^+$ = 198.1620, found = 198.1631

7-Allyloxy-2-ethylhept-2-enal (63)



To 4Å molecular sieve (22 g) and silica gel (22 g), both pre-dried in the oven and cooled under vacuum, was added pyridium chlorochromate (50 g, 0.23 mol) and dry CH_2Cl_2 (200 mL). The suspension was stirred at 0 °C for 10 minutes prior to addition of **65** (15.3 g, 0.08 mol) pre-diluted with dry CH_2Cl_2 (50 mL) dropwise. The mixture was allowed to stir at 0 °C for 6 hours prior to work-up. The reaction mixture was filtered through a sintered glass funnel packed with silica gel and washed with copious CH_2Cl_2. The filtrate was dried over anhydrous $MgSO_4$. The solvent was removed *in vacuo*. Product **63** was obtained in 84% (13.1 g) yield.

$\mathbf{R_f}$ = 0.52 (Hexane:EtOAc, 4:1);

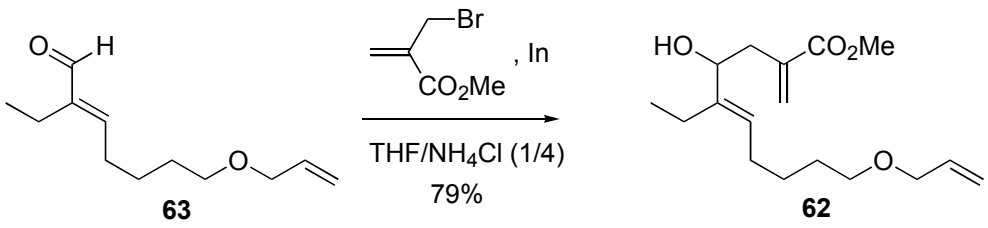
^{1}H NMR (300 MHz, $CDCl_3$): δ 0.93 (3H, t, *J* = 7.67 Hz, C**H**$_3$CH$_2$-), 1.51-1.67 (4H, m, -CH$_2$C**H**$_2$C**H**$_2$CH$_2$), 2.22 (2H, q, *J* = 7.67 Hz, -C**H**$_2$CH$_3$), 2.36 (2H, q, *J* = 7.15 Hz, -C=CHC**H**$_2$), 3.43 (2H, t, *J* = 7.42 Hz, -C**H**$_2$O-allyl), 3.92-3.94 (2H, m, -OC**H**$_2$CH=CH$_2$), 5.14 (1H, dd, *J* = 1.61, 10.2 Hz, -CH=C**H**$_2$), 5.24 (1H, dd, *J* = 17.3, 1.61 Hz, CH=C**H**$_2$), 5.81-5.95 (1H, m, -C**H**=CH$_2$), 6.40 (1H, t, *J* = 7.50 Hz, -C=CHC**H**$_2$), 9.32 (1H, s, -C**H**O) ppm;

^{13}C NMR (75 MHz, $CDCl_3$): δ 13.1 (-CH$_2$**C**H$_3$), 17.1 (-**C**H$_2$CH$_3$), 25.3 (-C=CH**C**H$_2$-), 28.3 (-C=CHCH$_2$**C**H$_2$-), 29.3 (-**C**H$_2$CH$_2$O-ally), 69.6 (-**C**H$_2$O-ally), 71.7 (-O**C**H$_2$CH=CH$_2$), 116.8 (-CH=**C**H$_2$), 134.7 (-**C**H=CH$_2$), 145.2 (-**C**=CHCH$_2$-), 154.2 (-C=**C**HCH$_2$-), 194.8 (-**C**HO) ppm;

FTIR (neat, cm^{-1}): 3420, 2975, 2868, 1710, 1458;

HRMS (EI [M]$^+$): *m/e* calculated for $[C_{12}H_{20}O_2]^+$ = 196.1463, found = 196.1437;

10-allyloxy-5-ethyl-4-hydrozy-2-methylene dec-5-enoic acid methyl ester (62)



63 (2.66 g, 13 mmol) in a solution of THF:NH_4Cl (1/4 v/v) (30 mL) was added indium powder mesh (3.1 g, 27 mmol) and methyl 2-(bromomethyl)acrylate (7.25 g, 40 mmol). The reaction mixture was allowed to stir vigorously for 24 hours at room temperature. 6N HCl was added to dissolve the white suspension. The reaction mixture was extracted with ethyl acetate (3 x 50 mL), washed with brine (2 x 50 mL) and dried over anhydrous $MgSO_4$. The solvent was removed *in vacuo*. Purification *via* column chromatography with 15% ethyl acetate in hexane gave the product **62** in 79% (3.04 g) yield.

$\mathbf{R}_f$ = 0.33 (Hexane:EtOAc, 4:1);

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.03 (3H, t, *J* = 7.63 Hz, -C**H**$_3$CH$_2$), 1.37-1.48 (2H, m, -C=CHCH$_2$C**H**$_2$), 1.56-1.65 (2H, m, -C**H**$_2$CH$_2$OCH$_2$), 1.98-2.19 (4H, m, CH$_3$C**H**$_2$-, -C=CHC**H**$_2$), 2.41-2.49 (1H, m, (OH)CHC**H**$_2$), 2.61-2.67 (1H, m, (OH)CHC**H**$_2$), 3.43 (2H, t, *J* = 6.42 Hz, C**H**$_2$O-allyl), 3.76 (3H, s, -OC**H**$_3$), 3.96 (2H, d, *J* = 5.63 Hz, -OC**H**$_2$CH=CH$_2$), 4.19 (1H, dd, *J* = 8.44, 1.60 Hz, -C**H**(OH)), 5.16 (1H, dd, *J* = 10.4, 1.60 Hz, -CH=C**H**$_2$), 5.27 (1H, dd, *J* = 10.2, 1.61 Hz, -CH=C**H**$_2$), 5.41 (1H, t, *J* = 7.23 Hz, -C=C**H**CH$_2$), 5.66 (1H, d, *J* = 1.20 Hz, -C=C**H**$_2$), 5.85-5.98 (1H, m, -C**H**=CH$_2$), 6.23 (1H, d, *J* = 1.60 Hz, -C=C**H**$_2$) ppm;

^{13}C NMR (75 MHz, $CDCl_3$): δ 14.2 (-CH$_2$**C**H$_3$), 20.6 (-**C**H$_2$CH$_3$), 26.3 (-C=CHCH$_2$**C**H$_2$-), 27.0 (-C=CH**C**H$_2$-), 29.4 (-**C**H$_2$CH$_2$O-ally), 39.3 (-**C**H$_2$CCO$_2$Me), 51.9 (O**Me**), 70.2 (-**C**H$_2$O-ally), 71.7 (-O**C**H$_2$CH=CH$_2$), 74.5 (-**C**HOH), 116.6 (-

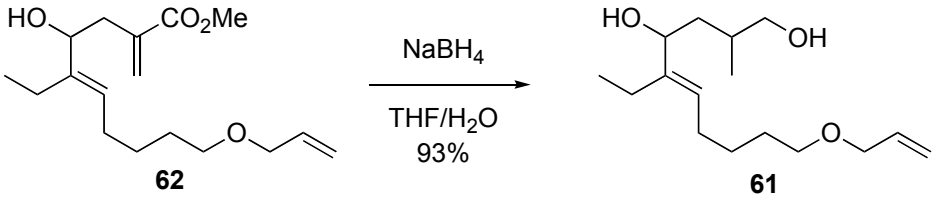
CH=**C**H_2), 125.6 (-C=**C**H_2), 127.6 (-C=**C**HCH_2-), 135.0 (-**C**H=CH_2), 137.4 (-**C**=CH_2), 142.8 (-**C**=$CHCH_2$-), 168.0 (-**C**=O) ppm;

FTIR (neat, cm^{-1}): 3432, 2933, 2858, 1718, 1438;

HRMS (ESI [M+Na]$^+$): *m/e* calculated for $[C_{17}H_{28}NaO_4]^+$ = 319.2, found = 318.9;

[M-OH]$^+$: *m/e* calculated for $[C_{15}H_{27}O_3]^+$= 279.2, found = 278.9;

10-Allyloxy-5-ethyl-2-methyl dec-5-ene-1,4-diol (61)



Lithium aluminium hydride in powder form (0.57 g, 14.9 mmol) was placed in a two-neck round bottom flask equipped with a Teflon-coated magnetic stirring bar under positive pressure nitrogen gas. Then, dry THF (25 mL) was injected, followed by the addition of **62** (2.44 g, 9.9 mmol) pre-diluted in dry THF (10 mL). The reaction mixture was refluxed for 2 hours. Saturated Na_2SO_4 was added to quench the reaction. The resulting mixture was stirred until white particles precipitated. The mixture was then passed through a sintered glass funnel and washed with CH_2Cl_2. The filtrate was dried over anhydrous $MgSO_4$ and the solvent was removed *in vacuo*. Purification *via* column chromatography with 50% ethyl acetate in hexane eluted the product **61** in 93% (2.49 g) yield.

R_f = 0.23 (Hexane:EtOAc, 4:1);

^{1}H NMR (300 MHz, $CDCl_3$): δ 0.88 (3H, d, *J* = 6.62 Hz, -C**H**$_3$CH), 0.98 (3H, t, *J* = 7.66 Hz, -C**H**$_3$CH_2), 1.37-1.44 (3H, m, -CHC**H**$_3$, -C=CHCH_2C**H**$_2$), 1.50-1.62 (2H, m, -C**H**$_2$CH_2OCH_2), 1.75-1.84 (2H, m, (OH)CHC**H**$_2$), 1.91-2.11 (4H, m, -CH_3C**H**$_2$, -C=CHC**H**$_2$), 2.95 (2H, brs, -O**H**), 3.39 (2H, t, *J* = 6.62 Hz, -C**H**$_2$O-allyl), 3.47-3.53

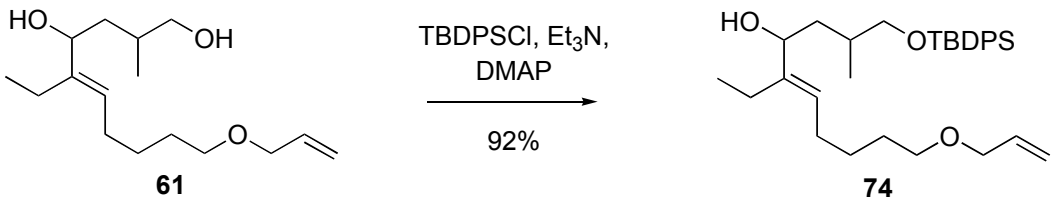
(1H, m, -C**H**OH), 3.69-3.73 (1H, m, -C**H**$_2$OH), 3.92 (2H, d, *J* = 5.57 Hz, -OC**H**$_2$CH=CH$_2$), 4.05 (1H, m, -C**H**$_2$OH), 5.13 (1H, dd, *J* = 10.5, 1.04 Hz, -CH=C**H**$_2$), 5.23 (1H, dd, *J* = 16.8, 1.75 Hz, -CH=C**H**$_2$), 5.35 (1H, t, *J* = 7.32 Hz, -C=C**H**CH$_2$), 5.81-5.94 (1H, m, -C**H**=CH$_2$) ppm;

^{13}C NMR (75 MHz, CDCl$_3$): δ 14.3 (-CH$_2$**C**H$_3$), 17.8 (-CH**C**H$_3$), 20.3 (-**C**H$_2$CH$_3$), 26.2 (-C=CHCH$_2$**C**H$_2$-), 27.0 (-C=CH**C**H$_2$-), 29.2 (-**C**HCH$_3$), 34.4 (-**C**H$_2$CH$_2$O-ally), 41.8 (-**C**H$_2$CHCH$_3$), 68.2 (-**C**H$_2$OH), 70.1 (-**C**H$_2$O-ally), 71.6 (-O**C**H$_2$CH=CH$_2$), 75.1 (-**C**HOH), 116.6 (-CH=**C**H$_2$), 125.0 (-C=**C**HCH$_2$-), 134.8 (-**C**H=CH$_2$), 144.2 (-**C**=CHCH$_2$-) ppm;

FTIR (neat, cm^{-1}): 3386, 2032, 2864, 1451;

HRMS (ESI) [M+Na]$^+$: *m/e* calculated for [C$_{16}$H$_{30}$NaO$_3$]$^+$ = 293.2, found = 293.3; [**M-C$_4$H$_9$O]$^+$):** *m/e* calculated for [C$_{12}$H$_{21}$O$_2$]$^+$ = 197.2, found = 197.2; [**M-C$_{11}$H$_{20}$O]$^+$:** *m/e* calculated for [C$_5$H$_{10}$NaO$_2$]$^+$ = 102.1, found = 102.2

10-Allyloxy-1-(*tert*-butyldiphenylsilanyloxy) -5-ethyl-2-methyl dec-5-en-4-ol (74)



61 **74**

61 (0.74 g, 2.73 mmol) and 4-dimethylamino pyridine (0.01 g, 0.16 mmol) in a 50 mL round bottom flask equipped with a Teflon coated magnetic stirring bar were dissolved in dry CH$_2$Cl$_2$ (20 mL). Triethylamine (0.38 mL, 2.73 mmol) was added in dropwise, followed by *t*-butyldiphenylsilylchloride (0.78 mL, 3.00 mmol) under 0 ºC. The reaction mixture was stirred for 24 hours at room temperature. The reaction was quenched by adding ice water (5 mL). The aqueous layer was extracted with CH$_2$Cl$_2$ (3 x 10 mL). The combined organic layer was washed with brine (2 x 10 mL) and

dried over anhydrous $MgSO_4$. The solvent was removed *in vacuo*. Purification *via* column chromatography with 5% ethyl acetate in hexane eluted the pure product **74** in 92% (1.28 g) yield.

$\mathbf{R_f}$ = 0.48 (Hexane:EtOAc, 4:1);

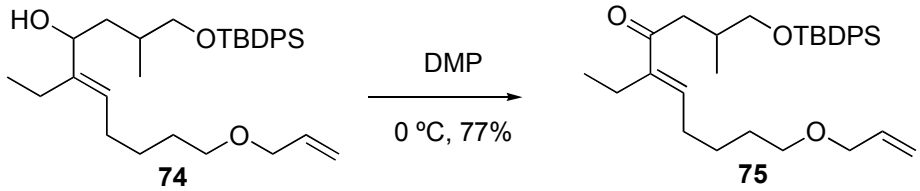
^{1}H NMR (300 MHz, $CDCl_3$): δ 0.93 (3H, d, *J* = 6.62 Hz, -C**H**$_3$CH), 1.01 (3H, t, *J* = 7.63 Hz, -C**H**$_3$CH$_2$), 1.06 (9H, s, -C(C**H**$_3$)$_3$), 1.27 (1H, brs, -O**H),** 1.39-1.48 (2H, m, (OH)CHC**H**$_2$), 1.56-1.67 (4H, m, -CH$_2$C**H**$_2$C**H**$_2$CH$_2$-), 1.82-1.92 (1H, m, -C**H**CH$_3$), 2.00-2.12 (4H, m, CH$_3$C**H**$_2$, -C=CHC**H**$_2$), 3.43 (2H, t, *J* = 6.43 Hz, -C**H**$_2$O-allyl), 3.51 (2H, d, *J* = 6.02 Hz, -C**H**$_2$OTBDPS), 3.96 (2H, d, *J* = 5.62 Hz, -OC**H**$_2$CH=CH$_2$), 4.07-4.11 (1H, m, -C**H**OH), 5.16 (1H, dd, *J* = 10.4, 1.60 Hz, -CH=C**H**$_2$), 5.26 (1H, dd, *J* = 17.4, 1.60 Hz, -CH=C**H**$_2$), 5.37 (1H, t, *J* = 7.22 Hz, -C=C**H**CH$_2$), 5.85-5.98 (1H, m, -C**H**=CH$_2$), 7.38-7.43 (6H, m, -Ph-**H**), 7.66-7.73 (4H, m, -Ph-**H**) ppm;

^{13}C NMR (75 MHz, $CDCl_3$): δ 14.1 (-**C**H$_3$), 17.2 (-**C**H$_3$), 19.2 (-**C**(CH$_3$)$_3$), 20.3 (-**C**H$_2$CH$_3$), 26.3 (-C=CHCH$_2$**C**H$_2$-), 26.5 (-C=CH**C**H$_2$-), 26.8 (-C(**C**H$_3$)$_3$), 29.4 (-**C**H$_2$CH$_2$O-ally), 33.2 (-**C**HCH$_3$), 40.7 (-**C**H$_2$CHCH$_3$), 69.4 (-**C**H$_2$OTBDPS), 70.2 (-**C**H$_2$O-ally), 71.7 (-O**C**H$_2$CH=CH$_2$), 74.6 (-**C**HOH), 116.6 (-CH=**C**H$_2$), 127.5 (-Ph-**C***o,p* x6), 129.5 (-**C**H=CH$_2$), 133.6 (-Ph-**C***q* x2), 134.7 (-**C**=CHCH$_2$-), 135.5 (-Ph-**C***m* x4) , 144.0 (-C=**C**HCH$_2$-) ppm;

FTIR (neat, cm^{-1}): 3412, 2930, 2856, 1421;

HRMS (ESI [M+Na]$^+$): *m/e* calculated for $[C_{32}H_{48}NaO_3Si]^+$ = 531.3373, found = 531.3270.

10-Allyloxy-1-(*tert*-butyldiphenylsilanyloxy) -5-ethyl-2-methyl dec-5-en-4-one (75)



74 **75**

To a solution of Dess-Martin reagent (3.20 g, 7.5 mmol) in anhydrous CH_2Cl_2 (15 mL) was added dropwise of **74** (2.54 g, 5 mmol) prediluted in CH_2Cl_2 (5 mL) at 0 °C. The reaction mixture was stirred under nitrogen at 0 °C for 3 hours. After completion, the reaction mixture was diluted with ether and poured slowly into a $Na_2S_2O_3$: $NaHCO_3$ (1:1) solution and stirred for 10 minutes and extracted with ether. The combined etherate was washed with $NaHCO_3$, brine and dried over anhydrous $MgSO_4$. Solvent was removed by concentration in *vacuo*. The residue was purified by flash chromatography on silica gel to provide **75** as a colorless oil, 1.95 g (77%).

$\mathbf{R_f}$ = 0.52 (Hexane:EtOAc, 4:1);

^{1}H NMR (300 MHz, $CDCl_3$): δ 0.89 (3H, d, *J* = 7.22 Hz, C**H**$_3$CH), 0.91 (3H, t, *J* = 7.23 Hz, C**H**$_3$CH$_2$), 1.05 (9H, s, C(C**H**$_3$)$_3$), 1.50-1.65 (4H, m, CH$_2$C**H**$_2$C**H**$_2$CH$_2$), 2.21-2.37 (6H, m, CH$_3$C**H**$_2$, C=CHC**H**$_2$, C**H**CH$_3$, O=CC**H**$_2$), 2.95 (1H, dd, *J* = 4.42, 14.5 Hz, O=CC**H**$_2$), 3.42 (2H, t, *J* = 6.00 Hz, C**H**$_2$O-allyl), 3.47-3.57 (2H, m, C**H**$_2$OTBDPS), 3.94 (2H, d, *J* = 5.62 Hz, OC**H**$_2$CH=CH$_2$), 5.14 (1H, dd, *J* = 10.4, 1.61 Hz, CH=C**H**$_2$), 5.24 (1H, dd, *J* = 17.3, 1.60 Hz, CH=C**H**$_2$), 5.82-5.95 (1H, m, C**H**=CH$_2$), 6.55 (1H, t, *J* = 7.23 Hz, C=C**H**CH$_2$), 7.31-7.39 (6H, m, -Ph-**H**), 7.62-7.67 (4H, m, -Ph-**H**) ppm;

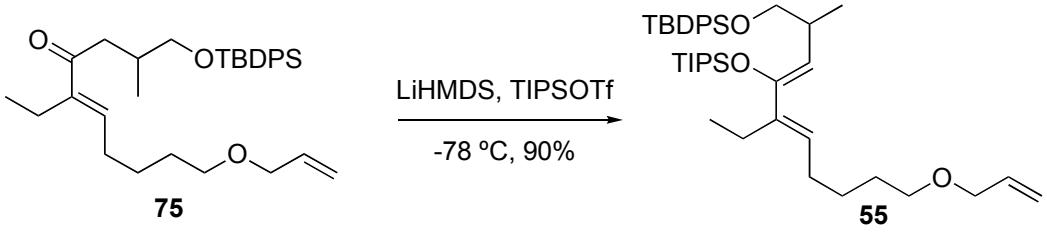
^{13}C NMR (75 MHz, $CDCl_3$): δ 13.8 (-**C**H$_3$), 16.7 (-**C**H$_3$), 18.8 (-**C**H$_2$CH$_3$), 19.2 (-**C**(CH$_3$)$_3$), 25.6 (-C=CHCH$_2$**C**H$_2$-), 26.8 (-C(**C**H$_3$)$_3$), 28.4 (-C=CH**C**H$_2$-), 29.4 (-**C**H$_2$CH$_2$O-ally), 33.0 (-**C**HCH$_3$), 40.7 (-**C**H$_2$CHCH$_3$), 68.3 (-**C**H$_2$OTBDPS), 69.9 (-

CH_2O-ally), 71.7 (-O**C**H_2CH=CH_2), 116.6 (-CH=**C**H_2), 127.5 (-Ph-**C***o,p* x6), 129.5 (-**C**H=CH_2), 133.6 (-Ph-**C***q* x2), 135.4 (-Ph-**C***m* x2), 141.8 (-C=**C**HCH_2-), 143.6 (-**C**=$CHCH_2$-), 201.1 (-**C**=O) ppm;

FTIR (neat, cm^{-1}): 2931, 2857, 1664, 1427;

HRMS (ESI [M+Na]$^+$): *m/e* calculated for $[C_{32}H_{46}NaO_3Si]^+$ = 529.3114, found = 529.3105;

10-Allyloxy-1-(*tert*-butyldiphenylsilanyloxy)-5-ethyl-2-methyl-4-(triisopropylsilanyloxy)-deca-3,5-diene (55)



Lithium hexamethyl disilazide (3.64 mL, 3.64 mmol) in THF (25 mL was cooled to -78 °C for 30 minutes. **75** (0.23 g, 0.46 mmol) prediluted in THF (5 mL) was added dropwise into the solution. The resulting mixture was stirred for 6 hours at -78 °C. Then, triisopropyl silyl triflate (0.61 mL, 2.28 mmol) was added dropwise under -78 °C. The reaction mixture was stirred at -78 °C for 30 minutes and gradually warmed to room temperature. The reaction was quenched at 0 °C with saturated $NaHCO_3$. A quarter of the solvent was removed in *vacuo*. The residue was extracted with ether (3 x 20 mL) and the combined organic layer was washed with saturated $NaHCO_3$ solution (2 x 15 mL) and dried over Mg_2SO_4. The solvent was removed in *vacuo*. Purification through flash column chromatography with 5% ethyl acetate in hexane eluted the pure compound **55** in 90% (0.27 g) yield.

$\mathbf{R}_f$ = 0.60 (Hexane:EtOAc, 4:1);

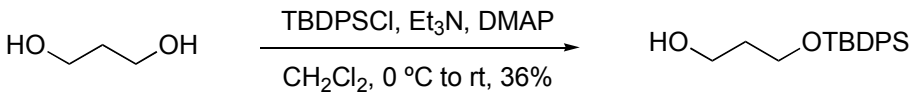
^{1}H NMR (300 MHz, $CDCl_3$): δ 1.07-1.11 (36H, m, -C(C**H**$_3$)$_3$, ((C**H**$_3$)$_2$CH) x3, ((CH$_3$)$_2$C**H**) x3, CHC**H**$_3$, CH$_2$C**H**$_3$), 1.41-1.51 (2H, m, C=CHCH$_2$C**H**$_2$), 1.59-1.68 (2H, m, CH$_2$C**H**$_2$ CH$_2$O), 2.05-2.22 (4H, m, CH$_3$C**H**$_2$, C=CHC**H**$_2$), 2.88-2.97 (1H, m, C**H**CH$_3$), 3.41-3.46 (3H, m, C**H**$_2$O-allyl, C**H**$_2$OTBDPS), 3.57-3.62 (1H, m, C**H**$_2$OTBDPS), 3.97 (2H, d, *J* = 5.57 Hz, OC**H**$_2$CH=CH$_2$), 4.62 (1H, d, *J* = 9.41 Hz, C=C**H**CH(CH$_3$)), 5.16 (1H, dd, *J* = 10.5, 1.40 Hz, CH=C**H**$_2$), 5.27 (1H, dd, *J* = 17.1, 1.75 Hz, CH=C**H**$_2$), 5.64 (1H, t, *J* = 7.23 Hz, C=C**H**CH$_2$), 5.85-5.98 (1H, m, C**H**=CH$_2$), 7.34-7.41 (6H, m, -Ph-**H**), 7.67-7.70 (4H, m, -Ph-**H**) ppm;

^{13}C NMR (75 MHz, $CDCl_3$): δ 12.3 (-**C**H(CH$_3$)$_2$), 13.8 (-**C**H$_3$), 17.7 (-CH(**C**H$_3$)$_2$), 18.2 (-C(**C**H$_3$)$_3$), 19.3 (-**C**(CH$_3$)$_3$), 21.2 (-**C**H$_2$-), 26.3 (-**C**H$_2$-), 26.8 (-**C**H$_3$), 27.6 (-**C**H$_2$-), 29.6 (-**C**H$_2$-), 68.5 (-**C**H$_2$OTBDPS), 70.2 (-**C**H$_2$O-ally), 71.8 (-O**C**H$_2$CH=CH$_2$), 111.6 (-**C**H=C-OTIPS), 116.7 (-CH=**C**H$_2$), 126.3 (-C=**C**HCH$_2$-), 127.5 (-Ph-**C***o* x4), 129.4 (-Ph-**C***p* x2), 134.1 (-Ph-**C***q* x2), 135.0 (-**C**H=CH$_2$), 135.7 (-Ph-**C***m* x4), 139.8 (-**C**=CHCH$_2$-), 150.8 (-CH=**C**-OTIPS) ppm;

FTIR (neat, cm^{-1}): 1658, 1651, 1634, 1384, 1366;

HRMS (EI [M+]$^+$): *m/e* calculated for $[C_{41}H_{66}O_3Si_2]^+$ = 662.4550, found = 662.4540;

3-(*tert*-butyldiphenylsilyloxy)propan-1-ol



To a stirred solution of 1,3-propanediol (31.6 g, 0.42 mol) in CH_2Cl_2 (500 mL) and pyridine (300 mL) was added DMAP (10.3 g, 0.084 mol). TBDPSCl (97.2 mL, 0.37 mol) was then added in dropwise at 0 ºC and left to stir for 3 hours. Saturated copper sulfate solution was added to remove the pyridine and the aqueous layer was extracted with CH_2Cl_2 (x3). The combined organic layer was washed with saturated $NaHCO_3$,

brine, dried, concentrated in *vacuo* and chromatographed to give 47.6 g of the mono-protected alcohol (36%).

$\mathbf{R_f}$ = 0.29 (Hexane:EtOAc 4:1);

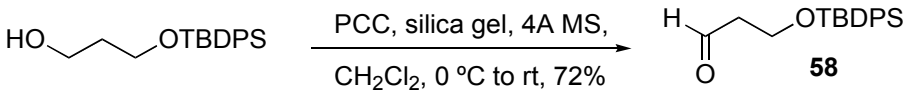
^{1}H NMR (300 MHz, $CDCl_3$): δ 1.11 (9H, s, -C(C**H**$_3$)$_3$), 1.30 (2H, q, *J* = 0.2 Hz, -C**H**$_2$-), 3.87 (4H, m, -C**H**$_2$O-), 7.43 (6H, m, -Ph-**H**), 7.70 (4H, m, -Ph-**H**) ppm;

^{13}C NMR (75 MHz, $CDCl_3$): δ 19.0 (-**C**(CH$_3$)$_3$), 26.7 (-C(**C**H$_3$)$_3$), 34.2 (-**C**H$_2$-), 61.8 (-O**C**H$_2$-), 63.1 (-O**C**H$_2$-), 127.5 (-Ph-**C** x4), 129.7 (-Ph-**C** x2), 133.2 (-Ph-**C** x4), 135.5 (-Ph-**C***q* x2) ppm;

FTIR (neat, cm^{-1}): 3418, 3070, 2989, 2856, 1636, 1472;

HRMS (EI [M-*t*Bu]$^+$): *m/e* calculated for $[C_{19}H_{26}O_2Si]^+$ = 257.1229, found = 257.0988;

3-(*tert*-butyldiphenylsilyloxy)propanal (58)



To a mixture of PCC (14.5 g, 66 mmol), 4Å molecular sieve powder (7 g) and silica gel (7 g) in anhydrous CH_2Cl_2 (200 mL) at 0 °C was added monoprotected alcohol (7 g, 22 mmol) prediluted in anhydrous CH_2Cl_2 (10 mL). The reaction mixture was stirred for 3 hours prior to workup. After completion (monitored by TLC), the reaction mixture was filtered through silica gel to afford the product **58** as a yellowish oil, 4.92 g (72%).

$\mathbf{R_f}$ = 0.48 (Hexane:EtOAc, 4:1);

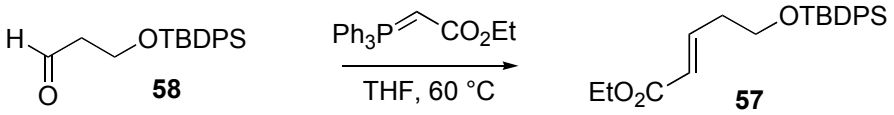
^{1}H NMR (300 MHz, $CDCl_3$): δ 0.88 (9H, s, -C(C**H**$_3$)$_3$), 2.60 (2H, t, *J* = 6.0 Hz, -C**H**$_2$CHO), 3.95 (2H, t, *J* = 6.0 Hz, -C**H**$_2$O-), 7.45-7.68 (10H, m, -Ph-**H**), 9.82 (1H, t, *J* = 2.1 Hz, -C**H**O) ppm;

^{13}C NMR (75 MHz, $CDCl_3$) δ 19.9 (-**C**$(CH_3)_3$), 26.7 (-C(**C**$H_3)_3$), 46.3 (-**C**H_2-), 59.5 (-O**C**H_2-), 127.6 (-Ph-**C** x4), 129.5 (-Ph-**C** x2), 133.2 (-Ph-**C** x4), 135.4 (-Ph-**C***q* x2), 202.1 (-**C**=O) ppm;

FTIR (neat, cm^{-1}): 3446, 3073, 3060, 2958, 2857, 1715, 1636, 1472;

HRMS (EI [M-*t*Bu]$^+$): *m/e* calculated for $[C_{19}H_{24}O_2Si]^+$ = 255.1072, found = 255.0858;

(*E*)-ethyl 5-(*tert*-butyldiphenylsilyloxy)pent-2-enoate (57)



To (15.0 g, 42 mmol) of preformed stabilized ylide and anhydrous sodium carbornate in dry THF (150 mL) was added the aldehyde **58** (8.7 g, 28 mmol) prediluted in dry THF (10 mL). The resulting mixture was then refluxed at 60 ºC for 24 hours. THF was later removed in *vacuo* and the residue chromatographed (hexane:ether = 70:30) giving 6.42 g of the α,β-unsaturated ester **57** as a yellow liquid (60%).

R_f = 0.56 (Hexane:EtOAc 4:1);

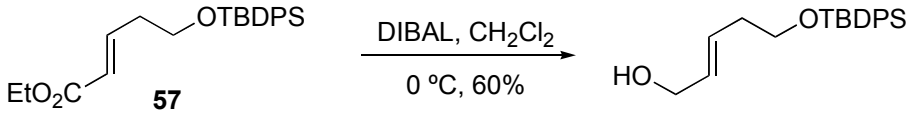
^{1}H NMR (300 MHz, $CDCl_3$): δ 1.02 (9H, s, -C(C**H**$_3)_3$), 1.28 (3H, t, *J* = 6.0 Hz, C**H**$_3$CH_2O-), 2.45 (2H, dt, *J* = 7.0, 6.6 Hz, -CH=CHC**H**$_2$), 3.80 (2H, q, *J* = 6.0 Hz, CH_3C**H**$_2$O-), 4.19 (2H, m, -C**H**$_2$O-), 5.85 (1H, d, *J* = 14.5 Hz, -C**H**=CH-), 6.95 (1H, dt, *J* = 8.3, 7.0 Hz, -CH=C**H**-), 7.40-7.66 (10H, m, -Ph-**H**) ppm

^{13}C NMR (75 MHz, $CDCl_3$): δ 14.3 (-**C**H_3), 19.1 (-**C**$(CH_3)_3$), 26.8 (-C(**C**$H_3)_3$), 35.4 (-**C**H_2-), 60.1 (-O**C**H_2-), 62.3 (-O**C**H_2-), 121.8 (-**C**H=CH-), 127.6 (-Ph-**C** x4), 129.5 (-Ph-**C** x2), 133.5 (-Ph-**C** x4), 134.8 (-Ph-**C***q* x2), 145.8 (-HC=**C**H-) , 166.4 (-**C**=O) ppm

FTIR (neat, cm^{-1}): 3422, 2931, 1721, 1654, 1427;

HRMS (EI [M-*t*Bu]$^+$): *m/e* calculated for $[C_{23}H_{30}O_3Si]^+$ = 325.1491, found = 325.1247;

(*E*)-5-(*tert*-butyldiphenylsilyloxy)pent-2-en-1-ol



To the ester **57** (2.48 g, 6.49 mmol) in anhydrous CH_2Cl_2 was added DIBAL (12 mL, 12 mmol, 1M in hexane solution) dropwise at 0 ºC. The reaction mixture was allowed to stir for 3 hours prior to quenching with saturated Na_2SO_4 at 0 ºC. The resulting slurry solution was filtered through a sintered glass funnel and washed with copious ether. The organic layers were dried over anhydrous $MgSO_4$ and concentrated in *vacuo* to give 1.33 g of the alcohol as a yellowish liquid (60%).

R$_f$ = 0.34 (Hexane:EtOAc, 4:1);

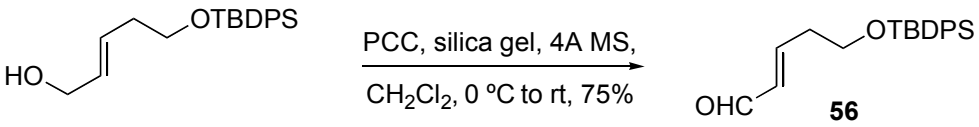
^{1}H NMR (300 MHz, CDCl$_3$): δ 1.05 (9H, s, -C(C**H**$_3$)$_3$), 2.55 (2H, t, *J* = 7.0 Hz, -C**H**$_2$OH), 3.45 (2H, t, *J* = 7.0 Hz, -C**H**$_2$O-), 4.03 (2H, m, -C**H**$_2$O-), 5.67 (2H, t, *J* = 4.5 Hz, -CH=C**H**-, -C**H**=CH-), 7.40-7.66 (10H, m, -Ph-**H**) ppm;

^{13}C NMR (75 MHz, CDCl$_3$): δ 19.1 (-**C**(CH$_3$)$_3$), 26.8 (-C(**C**H$_3$)$_3$), 35.5 (-**C**H$_2$-), 63.4 (-O**C**H$_2$-), 65.4 (-O**C**H$_2$-), 127.5 (-Ph-**C** x4), 128.3 (-**C**H=CH-), 129.5 (-Ph-**C** x2), 130.9 (-HC=**C**H-), 133.8 (-Ph-**C** x4), 135.5 (-Ph-**C***q* x2) ppm;

FTIR (neat, cm^{-1}): 3421, 3071, 2958, 2858, 1659, 1472;

HRMS (EI [M-*t*Bu]$^+$): *m/e* calculated for $[C_{21}H_{28}O_2Si]^+$ = 283.1155, found = 283.1162

(*E*)-5-(*tert*-butyldiphenylsilyloxy)pent-2-enal (56)



To a mixture of PCC (2.44 g, 11.33 mmol), 4Å molecular sieve powder (1.5 g) and silica gel (1.5 g) in anhydrous CH_2Cl_2 (15 mL) at 0 °C was added monoprotected alcohol (1.5 g, 3.78 mmol) prediluted in anhydrous CH_2Cl_2 (3 mL). The reaction mixture was stirred for 3 hours prior to workup. After completion (monitored by TLC), the reaction mixture was filtered through silica gel to afford the product **56** as a yellowish liquid, 1.15 g (75%).

R_f = 0.79 (Hexane:EtOAc, 4:1);

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.00 (9H, s, -C(C**H**$_3$)$_3$), 2.55 (2H, m, -CH=CHC**H**$_2$-), 3.83 (2H, t, *J* = 6.1 Hz, -C**H**$_2$O-), 6.15 (1H, dd, *J* = 15.0, 6.0 Hz, -C**H**=CH-), 6.83 (1H, dt, *J* = 15.0, 6.0 Hz, -CH=C**H**-), 7.40-7.64 (10H, m, -Ph-**H**), 9.46 (1H, d, *J* = 6.0 Hz, -C**H**O) ppm;

^{13}C NMR (75 MHz, $CDCl_3$): δ 19.2 (-**C**(CH$_3$)$_3$), 26.8 (-C(**C**H$_3$)$_3$), 63.5 (-O**C**H$_2$-), 127.6 (-Ph-**C** x4), 129.8 (-Ph-**C** x2), 133.4 (-Ph-**C** x4), 133.5 (-CH=**C**H-), 135.5 (-Ph-**C***q* x2), 155.4 (-**C**H=CH-), 193.9 (-**C**=O) ppm;

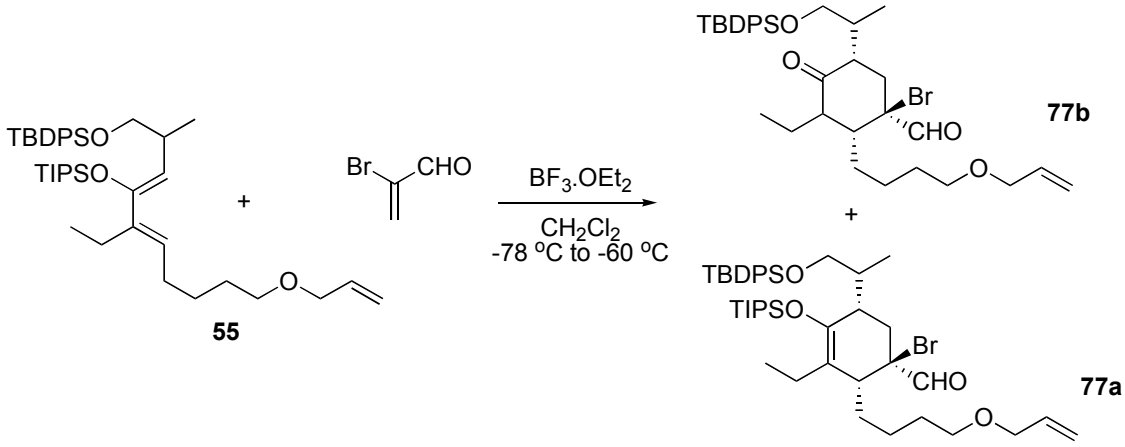
FTIR (neat, cm^{-1}): 3422, 1694, 1654;

HRMS (EI [M-*t*Bu, -2C_6H_6]$^+$): *m/e* calculated for $[C_5H_7O_2Si]^+$ = 127.1385, found = 127.0413;

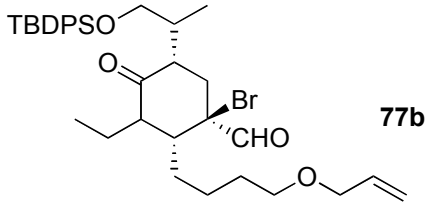
General procedure for Diels-Alder reaction:

To a stirred solution of dienophile (1.0 mmol), a proton scavenger, 2,6-di-*tert*-butylpyridine (0.11 mL, 0.5 mmol) and 4Å molecular sieve (100 mg, excess) at -78 ºC in CH_2Cl_2 (1 mL) was added dropwise boron trifluoride dietherate (0.03 mL, 0.25 mmol). Subsequently, the pre-diluted diene (0.5 mmol) in CH_2Cl_2 (1 mL) was added dropwise. The whole reaction was stirred at -78 ºC to -60 ºC for 16 hours prior to workup. The reaction was quenched with saturated $NaHCO_3$ (2 mL). The organic layer was extracted with CH_2Cl_2 (3 x 5 mL), washed with saturated $NaHCO_3$ (2 x 5 mL), and dried over anhydrous $MgSO_4$. The filtrate was filtered and concentrated. Purification with flash column chromatography afforded the pure compound.

Scheme 3-21



2-(4-(allyloxy)butyl)-1-bromo-5-(1-(*tert*-butyldiphenylsilyloxy)propan-2-yl)-3-ethyl-4-oxocyclohexanecarbaldehyde (77b)



Yield = 45%

R_f = 0.45 (Hexane:EtOAc, 4:1);

^{1}H NMR (300 MHz, $CDCl_3$): δ 0.65 (3H, d, *J* = 6.62 Hz, -CHC**H**$_3$), 0.86 (3H, t, *J* = 7.32 Hz, -CH_2C**H**$_3$), 1.04-1.07 (11H, m, -C(C**H**$_3$)$_3$), -C**H**$_2$-CBr-), 1.49-1.69 (6H, m, C**H**$_2$C**H**$_2$$CH_2$O-allyl, C**H**$_2$$CH_3$), 1.81-1.90 (2H, m, -CHC**H**$_2$-), 1.95-2.12 (1H, m, -C**H**-C=O), 2.23-2.32 (1H, m, -C**H**-$CH_2$$CH_3$), 2.33-2.41 (1H, m, -C**H**CH_3), 2.58-2.66 (1H, td, *J* = 9.41, 3.83 Hz, -C**H**-CBr-), 3.37-3.46 (3H, m, C**H**$_2$O-allyl, TBDPSOC**H**$_2$), 3.55-3.59 (1H, m, TBDPSOC**H**$_2$), 3.95-3.97 (2H, d, *J* = 4.18 Hz, OC**H**$_2$CH=CH_2), 5.18 (1H, dd, *J* = 10.5, 1.39 Hz, CH=C**H**$_2$), 5.26 (1H, dd, *J* = 17.5, 1.39 Hz, -CH=C**H**$_2$), 5.85-5.96 (1H, m, -C**H**=CH_2), 7.39-7.43 (6H, m, -Ph-**H**), 7.62-7.63 (4H, m, -Ph-**H**), 9.51 (1H, s, C**H**O) ppm;

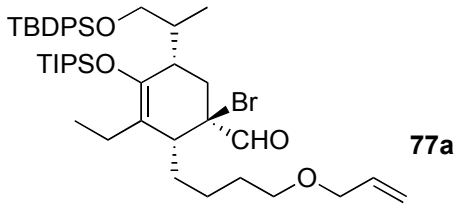
^{13}C NMR (75 MHz, $CDCl_3$): δ 11.2 (-**C**H_3), 12.3 (-**C**H_3), 15.9 (-**C**H_2-), 19.2 (-**C**$(CH_3)_3$), 22.3 (-**C**H_2-), 23.4 (-**C**H_2-), 26.5 (-**C**H_2-), 26.9 (-C(**C**H_3)$_3$), 29.3 (-**C**H_2-), 34.9 (-**C**H-), 36.6 (-**C**H-), 39.1 (-**C**H-), 42.9 (-**C**H), 53.8 (-**C**-CHO), 66.7 (-O**C**H_2-), 69.9 (-O**C**H_2-), 71.8 (-O**C**H_2-), 116.8 (-CH=**C**H_2), 127.7 (-Ph-**C***m* x4), 129.6 (-Ph-**C***o* x4), 133.6 (-Ph-**C***q* x2), 134.8 (-**C**H=CH_2), 135.5 (-Ph-**C***p* x2), 199.5 (-**C**HO), 213.7 (-**C**=O) ppm;

FTIR (neat, cm^{-1}): 3071, 2932, 2774, 2741, 1724, 1696, 1472;

HRMS (ESI) [M+Na]$^+$: *m/e* calculated for $[C_{35}H_{49}BrNaO_4Si]^+$ = 663.3 found = 663.3;

[M-Br]$^+$: *m/e* calculated for $[C_{12}H_{21}O_2]^+$ = 561.2 found = 521.2;

2-(4-(allyloxy)butyl)-1-bromo-5-(1-(*tert*-butyldiphenylsilyloxy)propan-2-yl)-3-ethyl-4-(triisopropylsilyloxy)cyclohex-3-enecarbaldehyde (77a)



77a

Yield = 28%

R_f = 0.68 (Hexane:EtOAc, 4:1);

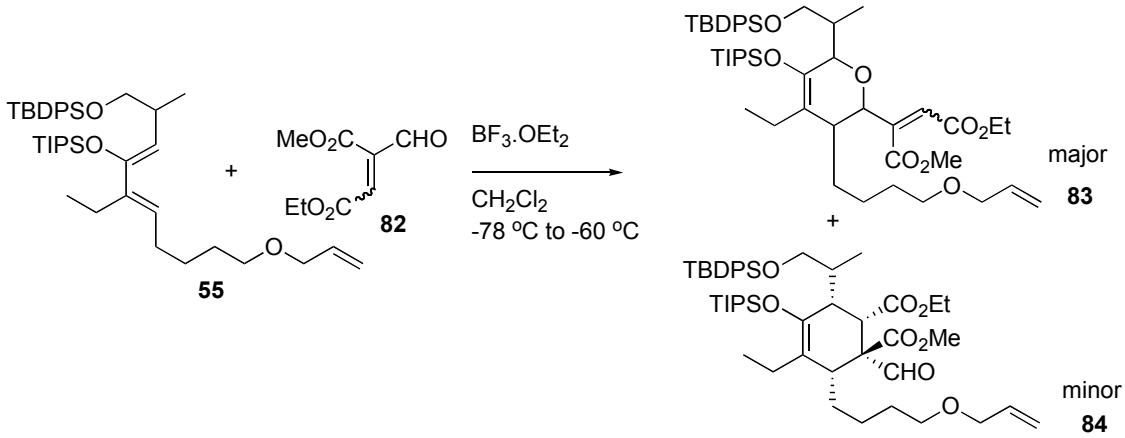
^{1}H NMR (300 MHz, $CDCl_3$): δ 0.91 (3H, d, *J* = 3.2 Hz, -CHC**H**$_3$), 0.98 (3H, t, *J* = 7.40 Hz, -CH_2C**H**$_3$), 1.03 (18 H, s, TIPS-), 1.05 (9H, s, -C(C**H**$_3$)$_3$), 1.08-1.48 (6H, m, C**H**$_2$C**H**$_2$C**H**$_2$$CH_2$O-allyl), 1.84-1.90 (1H, m, -C**H**CH_3), 1.95-2.12 (3H, m, -C**H**-C**H**$_2$-CBr-), 2.17-2.54 (5H, m, 3C**H**$(CH_3)_2$, C**H**$_2$$CH_3$), 2.56 (1H, brs, -C**H**-CBr-), 3.21 (2H, dt, *J* = 6.25, 1.4 Hz, -C**H**$_2$O-allyl), 3.35 (1H, t, *J* = 8.8 Hz, TBDPSOC**H**$_2$-), 3.59 (1H, dd, *J* = 9.47, 3.25 Hz, TBDPSOC**H**$_2$-), 3.86 (2H, d, *J* = 5.5 Hz, -OC**H**$_2$CH=CH_2), 5.15 (1H, dd, *J* = 10.15, 1.4 Hz, -CH=C**H**$_2$), 5.23 (1H, dd, *J* = 17.1, 1.85 Hz, CH=C**H**$_2$), 5.83-5.90 (m, 1H, -C**H**=CH_2), 7.33-7.36 (6H, m, -Ph-**H**), 7.60-7.62 (4H, m, -Ph-**H**), 9.43 (1H, s, -C**H**O) ppm;

^{13}C NMR (75 MHz, $CDCl_3$): δ 11.9, 12.0, 13.7, 15.2, 18.0, 18.2, 19.2, 22.0, 26.0, 26.8, 27.2, 29.7, 33.9, 34.9, 41.2, 45.4, 65.2, 69.5, 71.7, 74.3, 116.6, 127.4, 127.5, 127.6, 129.4, 133.6, 134.8, 135.4, 135.5, 144.8, 167.7, 190.9 ppm;

FTIR (neat, cm^{-1}): 3071, 2932, 2774, 2741, 1724, 1696, 1472;

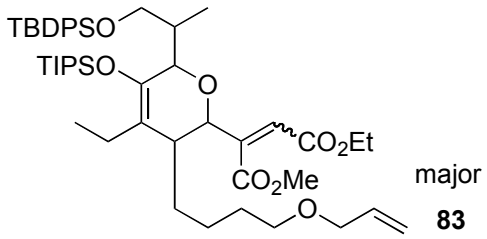
HRMS (ESI) $[M+Na]^+$: *m/e* calculated for $[C_{44}H_{69}BrNaO_4Si_2]^+$ = 819.3815 found = 819.3812;

Scheme 3-22



Combined yield = 35% (hetero : normal = 5:1)

4-ethyl 1-methyl 2-(3-(4-(allyloxy)butyl)-6-(1-(*tert*-butyldiphenylsilyloxy)propan-2-yl)-4-ethyl-5-(triisopropylsilyloxy)-3,6-dihydro-2*H*-pyran-2-yl)but-2-enedioate (83)



^{1}H NMR (500 MHz, $CDCl_3$): δ 0.58 (3H, t, *J* = 7.4 Hz, -$CH_2C\mathbf{H}_3$), 1.03 (29 H, brs, -$C(C\mathbf{H}_3)_3$), -$CH(C\mathbf{H}_3)_2$ x3, -$CHCH_2CH_2C\mathbf{H}_2CH_2$Oally), 1.17 (3H, d, *J* = 6.95 Hz, -$CHC\mathbf{H}_3$), 1.29-1.33 (1H, m, -$C\mathbf{H}_2CH_3$), 1.31 (3H, t, *J* = 6.95 Hz, -$OCH_2C\mathbf{H}_3$), 1.34-1.64 (7H, m, -$C\mathbf{H}(CH_2)_2$ x3, -$CHC\mathbf{H}_2C\mathbf{H}_2CH_2CH_2$Oally), 1.99 (1H, brs, -$C\mathbf{H}(CH_2)_4$Oally), 2.05-2.12 (1H, m , -$C\mathbf{H}CH_3$), 2.41 (1H, dt, *J* = 7.4, 13.85 Hz, -$C\mathbf{H}_2CH_3$), 3.37-3.42 (3H, m, -$C\mathbf{H}_2$O-ally, -$OC\mathbf{H}$-CH-CH_3, -$C\mathbf{H}_2$OTBDPS), 3.74 (3H, s, -$CO_2\mathbf{Me}$), 3.75-3.78 (1H, m, -$C\mathbf{H}_2$OTBDPS), 3.88 (1H, dd, *J* = 9.25, 2.8 Hz, -$C\mathbf{H}_2$O-ally), 3.95 (2H, dt, *J* = 5.5, 1.35 Hz, -$OC\mathbf{H}_2CH{=}CH_2$), 4.22 (2H, q, *J* = 6.95 Hz, -$OC\mathbf{H}_2CH_3$), 4.51 (1H, t, *J* = 2.35 Hz, -$OC\mathbf{H}$-C=C-CO_2Et), 5.16 (1H, dq, *J* = 10.43, 1.35 Hz, -CH=C$\mathbf{H}_2$), 5.26 (1H, dq, *J* = 17.32, 1.85 Hz, -CH=C$\mathbf{H}_2$), 5.87-5.96

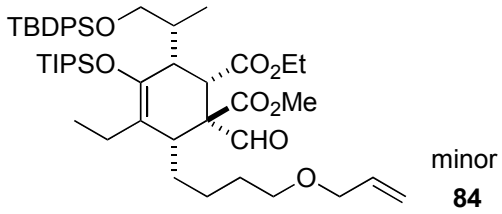
(1H, m, -C**H**=CH_2), 6.25 (1H, d, *J* = 2.3 Hz, -C=C**H**-CO_2Et), 7.31-7.38 (6H, m, Ph-**H**), 7.61-7.65 (4H, m, Ph-**H**) ppm;

^{13}C NMR (125 MHz, $CDCl_3$): δ 12.1 (-**C**H_3), 13.5 (-**C**H$(CH_3)_2$- x3), 14.1 (-**C**H_3), 17.9 (-CH(**C**$H_3)_2$ x3), 18.6 (-**C**H_3), 19.3 (-**C**H_2-), 19.5 (-**C**$(CH_3)_3$), 23.3 (-**C**H_2-), 26.9 (-C(**C**$H_3)_3$), 29.4 (-**C**H_2-), 30.9 (-**C**H_2-), 35.0 (-**C**H-), 45.5 (-**C**H-), 52.1 (-O**Me**), 60.8 (-O-**C**H_2-), 67.7 (-O-**C**H_2-), 70.3 (-O-**C**H_2-), 71.1 (-O-**C**H-), 71.7 (-O-**C**H_2-), 74.1 (-O-**C**H-), 116.6 (-CH=**C**H_2), 118.5 (-C=**C**-), 122.0 (-C=**C**H-), 127.4 (Ph-**C***m* x4), 129.2 (Ph-**C***p* x2), 134.3 (Ph-**C***q* x2), 135.0 (-C=**C**H-), 135.5 (Ph-**C***o* x4), 143.4 (-C=**C**-), 146.3 (-**C**=C-), 165.6 (**C**=O), 166.9 (**C**=O) ppm;

FTIR (neat, cm^{-1}): 3426, 2931, 2864, 1730, 1651, 1463, 1428;

HRMS (ESI) [M+H]$^+$: *m/e* calculated for $[C_{49}H_{77}O_8Si_2]^+$ = 849.5157 found = 849.5163;

2-ethyl 1-methyl 6-(4-(allyloxy)butyl)-3-((*S*)-1-(*tert*-butyldiphenylsilyloxy)propan-2-yl)-5-ethyl-1-formyl-4-(triisopropylsilyloxy)cyclohex-4-ene-1,2-dicarboxylate (84)



minor

84

Diastereoselectivity: 76:24;

^{1}H NMR (500 MHz, $CDCl_3$): δ 0.91-1.04 (33H, m, -CHC**H**$_3$, -C(C**H**$_3)_3$), -C**H**$(CH_3)_2$ x3, -CH(C**H**$_3)_2$ x3), 0.85 (3H, t, *J* = 7.4 Hz, -CH_2C**H**$_3$), 1.28 (3H, dd, *J* = 6.95, 7.4 Hz, -OCH_2CH_3), 1.26-1.40 (4H, m, -CHC**H**$_2$C**H**$_2$$CH_2CH_2$Oally), 1.50 (1H, quintet, *J* = 6.95 Hz, -C**H**$_2$$CH_2$Oally), 1.68-1.78 (2H, m, -C**H**$_2$$CH_3$, -C**H**$_2$$CH_2$O-ally), 1.80-1.89 (1H, m, -C**H**CH_3), 2.12 (1H, dq, *J* = 14.3, 7.4 Hz, -C**H**$_2$$CH_3$), 2.43 (1H, brs, -

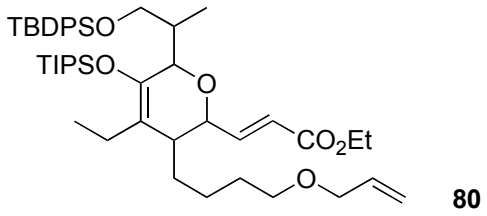
C**H**C(CHO)), 2.48 (1H, dd, *J* = 5.55, 5.05 Hz, -C**H**CHCO$_2$Et), 3.37 (2H, t, *J* = 6.45 Hz, -C**H**$_2$Oally), 3.47 (1H, d, *J* = 10.1 Hz, -C**H**$_2$OTBDPS), 3.56 (1H, d, *J* = 5.1 Hz, -C**H**CO$_2$Et), 3.63 (1H, dd, *J* = 10.1, 4.15 Hz, -C**H**$_2$OTBDPS), 3.76 (3H, s, CO$_2$**Me**), 3.94 (2H, dt, *J* = 5.55, 1.4 Hz, -OC**H**$_2$CH=CH$_2$), 4.11 (1H, dd, *J* = 10.65, 6.95 Hz, -OC**H**$_2$CH$_3$), 4.22 (1H, dd, *J* = 10.65, 7.4 Hz, -OC**H**$_2$CH$_3$), 5.15 (1H, dq, *J* = 12.02, 1.4 Hz, -CH=C**H**$_2$), 5.25 (1H, dq, *J* = 17.1, 1.35 Hz, -CH=C**H**$_2$), 5.86-5.94 (1H, m, -C**H**=CH$_2$), 7.30-7.39 (6H, m, Ph-**H**), 7.61-7.68 (4H, m, Ph-**H**), 10.21 (1H, s, -C**H**O) ppm;

^{13}C NMR (125 MHz, CDCl$_3$): δ 13.5 (-CH$_2$**C**H$_3$), 13.7 (-**C**H(CH$_3$)$_2$ x3), 13.9 (-OCH$_2$**C**H$_3$), 17.5 (-CH**C**H$_3$), 18.1 (-CH(**C**H$_3$)$_2$ x3), 19.3 (-**C**(CH$_3$)$_3$), 21.1 (-**C**H$_2$CH$_3$), 26.9 (-C(**C**H$_3$)$_3$), 28.4 (-CH**C**H$_2$CH$_2$CH$_2$CH$_2$O-ally), 29.3 (-CHCH$_2$**C**H$_2$CH$_2$CH$_2$Oally), 29.8 (-CHCH$_2$CH$_2$**C**H$_2$CH$_2$O-ally), 37.7 (-**C**HCH$_3$), 44.2 (-**C**HCHCO$_2$Et), 45.1 (-H**C**C-CHO), 52.1 (-**C**HCO$_2$Et), 52.7 (O**Me**), 61.0 (-O**C**H$_2$CH$_3$), 61.5 (**C**-CHO), 66.4 (-**C**H$_2$OTBDPS), 69.9 (-**C**H$_2$O-ally), 71.8 (-O**C**H$_2$CH=CH$_2$), 116.6 (CH=**C**H$_2$), 119.9 (-C=**C**-CH$_2$CH$_3$), 127.4 (Ph-**C***m* x2), 127.5 (Ph-**C***m* x2), 129.2 (Ph-**C***p*), 129.3 (Ph-**C***p*), 134.0 (Ph-**C***q*), 134.4 (Ph-**C***q*), 135.0 (**C**H=CH$_2$), 135.6 (Ph-**C***o* x2), 135.7 (Ph-**C***o* x2), 143.3 (**C**-TIPSO), 172.4 (**C**O$_2$Et), 173.0 (**C**O$_2$Me), 197.6 (-**C**HO) ppm;

FTIR (neat, cm^{-1}): 3426, 2931, 2864, 1730, 1651, 1463, 1428;

HRMS (ESI) [M+Na]$^+$: *m/e* calculated for [C$_{49}$H$_{76}$NaO$_8$Si$_2$]$^+$ = 871.4976 found = 871.4972;

(*E*)-ethyl 3-(3-(4-(allyloxy)butyl)-6-(1-(*tert*-butyldiphenylsilyloxy)propan-2-yl)-4-ethyl-5-(triisopropylsilyloxy)-3,6-dihydro-2*H*-pyran-2-yl)acrylate (80)



80

R_f = 0.71 (Hexane:EtOAc, 4:1);

Yield = 77%

^{1}H NMR (500 MHz, $CDCl_3$): δ 0.81 (3H, t, *J* = 7.45 Hz, -CH_2C**H**$_3$), 0.95-1.10 (30H, m, -C(C**H**$_3$)$_3$), -C**H**(C**H**$_3$)$_2$ x3), 1.22-1.33 (6H, m, -C**H**$_2$-, -C**H**-, -C**H**$_3$), 1.54-1.80 (4H, m, -C**H**$_2$- x2), 1.97-2.15 (3H, m, -C**H**$_3$), 3.37-3.52 (3H, m, -OC**H**- x3), 3.66-3.73 (1H, m, -OC**H**-), 3.94 (2H, t, *J* = 5.55 Hz, -OC**H**$_2$CH=CH_2), 4.02 (1H, d, *J* = 9.00 Hz, -OC**H**-), 4.16 (2H, q, *J* = 7.05 Hz, -OC**H**$_2$-), 4.22-4.29 (1H, m, -OC**H**-), 5.14 (1H, d, *J* = 10.30 Hz, -CH=C**H**$_2$), 5.26 (1H, d, *J* = 17.35 Hz, -CH=C**H**$_2$), 5.86-5.95 (1H, m, -C**H**=CH_2), 6.10 (1H, dd, *J* = 15.45, 2.30 Hz, -C**H**=CH-CO_2Et), 6.91-6.98 (1H, m, -CH=C**H**-CO_2Et), 7.30-7.37 (6H, m, Ph-**H**), 7.59-7.62 (4H, m, Ph-**H**) ppm;

^{13}C NMR (125 MHz, $CDCl_3$): δ 12.6 (-**C**H_3), 13.5 (-**C**H(CH_3)$_2$- x3), 15.5 (-**C**H_3), 18.0 (-CH(**C**H_3)$_2$ x3), 18.7 (-**C**(CH_3)$_3$), 18.9 (-**C**H_3), 19.0 (-**C**H_2-), 19.1 (-**C**H_2-), 22.3 (-**C**H_2-), 26.8 (-C(**C**H_3)$_3$), 29.6 (-**C**H_2-), 35.5 (-**C**H-), 46.3 (-**C**H-), 60.1 (-O**C**H_2-), 67.9 (-O**C**H_2-), 70.3 (-O**C**H_2-), 71.7 (-O**C**H_2-), 75.2 (-O**C**H-), 76.3 (-O**C**H-), 116.5 (-CH=**C**H_2), 118.5 (-C=**C**-), 119.8 (-HC=**C**H-), 127.4 (Ph-**C***m* x4), 129.2 (Ph-**C***p* x2), 133.9 (Ph-**C***q* x2), 135.0 (-C=**C**H-), 135.4 (Ph-**C***o* x4), 144.2 (-C=**C**-), 147.0 (-**C**H=CH-), 166.3 (**C**=O) ppm

APPENDIX

Silicon-assisted Propargylic Transfer to Aldehydes

A.1 Introduction

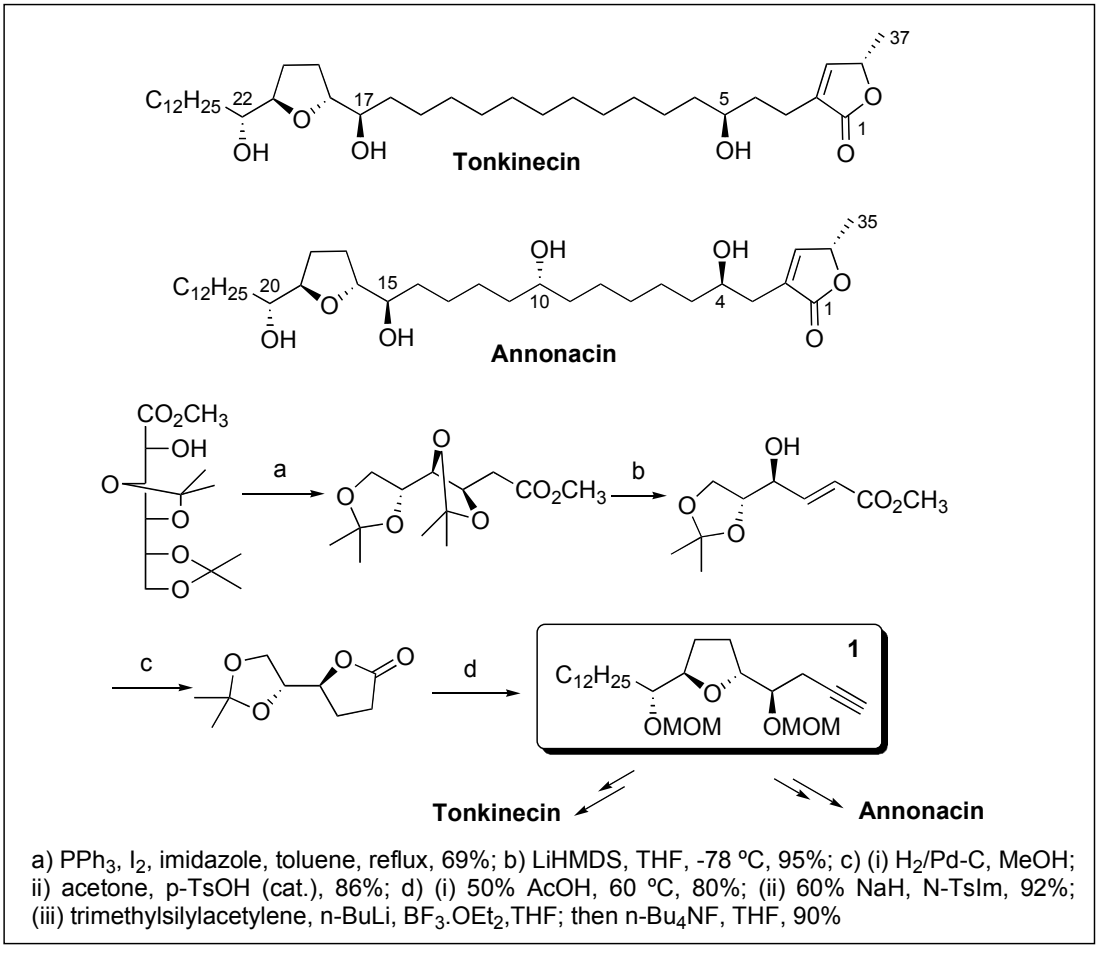
The control of the carbon-carbon bonds formation with good and predictable control of stereochemistry is one of the most crucial area in organic synthesis, especially in natural product synthesis and drug design. The allylation and the propargylation/allenylation of aldehydes and ketones (carbonyls) with organometallic reagents are among the most fundamental and important reactions for constructing carbon-carbon bonds.[1] The synthetically attractive point of the methodology using propagyl/allenyl as intermediate comes from the tendency of such unique nucleophiles to produce mixture of both homopropargylic and allenic species at the same time.

Allenic and propargylic alcohols are attractive intermediates in organic synthesis because of their unique structural characteristics and versatile nature.[1] They have been used extensively as important building blocks for the synthesis of many biologically active natural products such as 3-deoxy-D-manno-2-octulosonic acids (KDO), 3-deoxy-D-glycero-D-galacto-2-ulosonic acids (KDN),[2] (±)-9-deoxygoniopypyrone[3] and mono-THF acetogenins.[4]

[1] For reviews, see: (a) Marshall, J. A. *Chem. Rev.* **2000**, *100,* 3163. (b) Yamamoto, H. in *Comprehensive Organic Synthesis Vol. 2* Ed.: Trost, B. M., Pergamon Press, Oxford, **1991**, Chapter 1.3. (c) Panek, J. S. in *Comprehensive Organic Synthesis Vol. 1* Ed.: Schreiber, S. L. Pergamon Press, Oxford, **1991**, p.595.
[2] Li, L. -S.; Wu, Y. -L. *Tetrahedron* **2002**, *58,* 9049.
[3] Friesen, R. W.; Bissada, S. *Tetrahedron Lett.* **1994**, *35,* 5615.
[4] Hu, T. -S.; Yu, Q.; Wu, Y. -L.; Wu, Y. -K. *J. Org. Chem.* **2001**, *66,* 853.

A.2 Propargylic Alcohols as Intermediates in Organic Synthesis

Recently, propargylic alcohols have been used extensively in natural product synthesis. In 2001, Wu and coworkers have reported the application of propargylic alcohol in the total synthesis of two mono-THF acetogenins, tonkinecin and annonacin. In their synthesis strategy, the homopropargylic alcohol **1** served as one of the key intermediate, which in turn was prepared from D-glucono-δ-lactone (Scheme A-1).[4]



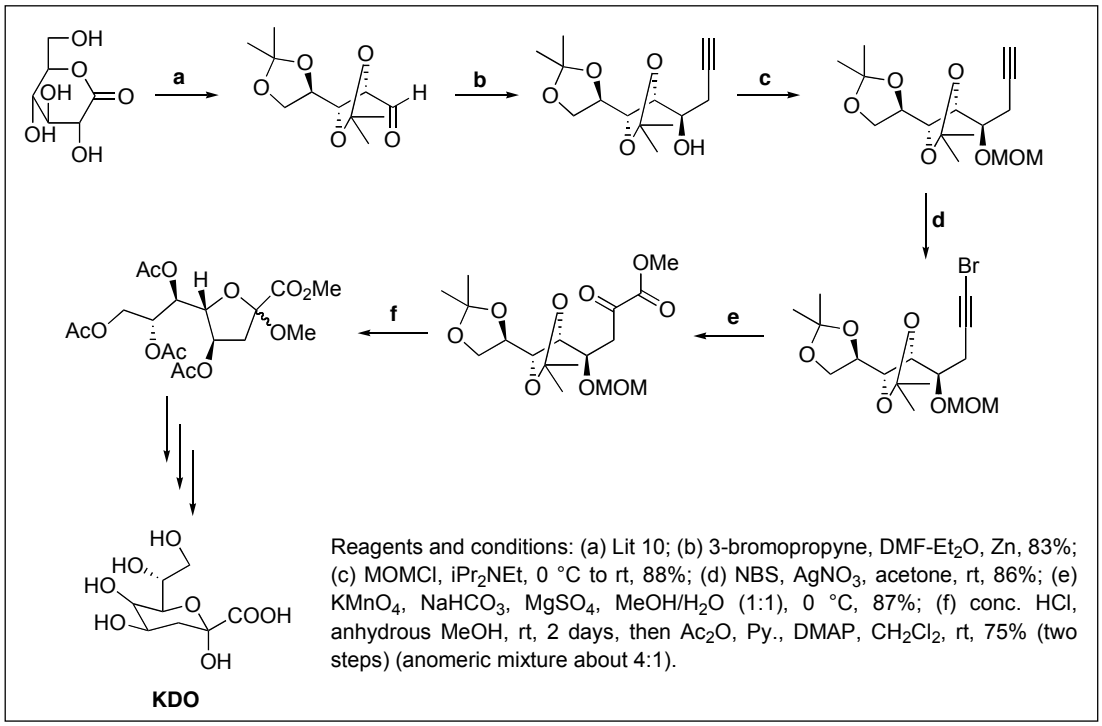
Scheme A-1 Total synthesis of tonkinecin and annonacin

[4] Hu, T. -S.; Yu, Q.; Wu, Y. -L.; Wu, Y. -K. *J. Org. Chem.* **2001**, *66,* 853.

Later in 2002, Wu and coworkers reported the synthesis of 3-deoxy-D-manno-2-octulosonic acids (KDO) and 4-*epi*-KDN in the furanose form from the readily available sugar in 41% and 35% yield respectively (Scheme A-2 and Scheme A-3).[5] The key step in their synthesis is the introduction of a pyruvate segment by asymmetric propargylation and oxidation of terminal alkynes.

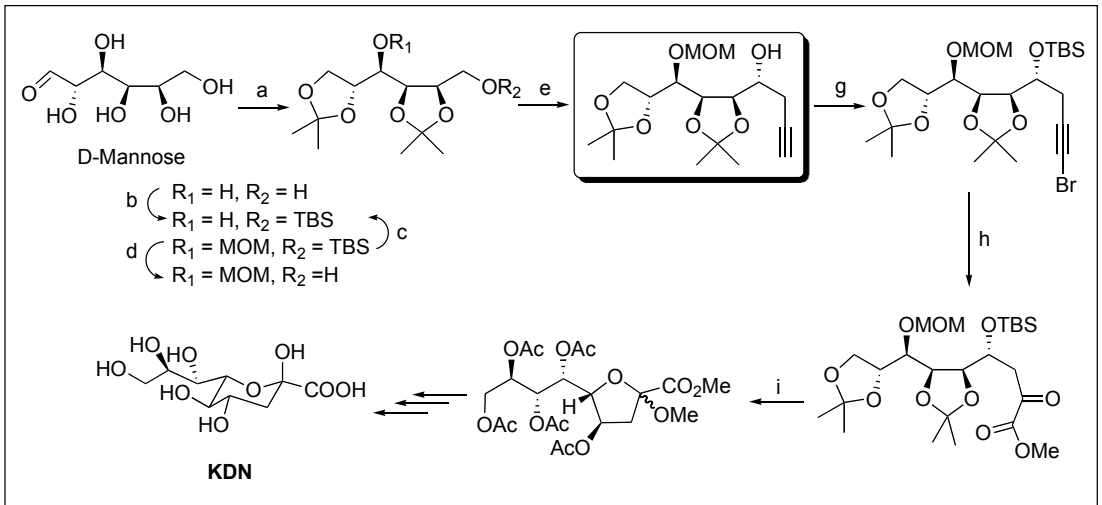
3-deoxy-D-manno-2-octulosonic acids (KDO) and 3-deoxy-D-glycero-D-galacto-2-ulosonic acids (KDN) possess a number of interesting biological activities. KDO is an essential constituent of the outer-cell membrane lipopolysaccharide of Gram-negative bacteria, and incorporation of KDO is likely to be a key step in the growth of these bacteria.[6] KDN is a deaminated sialic acid first isolated in 1986 by Inoue and co-workers[7] from the membrane polysialoglycoproteins of rainbow trout eggs. It has been found that KDN is likely to be responsible for protection of the egg membrane from attacks by bacterial sialidases.[8] A more recent discovery shows that free KDN occurs at elevated levels in human fetal cord red blood cells and ovarian cancer cells.[9]

[5] (a) Li, L. -S.; Wu, Y. -L. *Tetrahedron Lett.* **2002**, *43,* 2427. (b) Li, L. -S.; Wu, Y. -L. *Tetrahedron* **2002**, *58,* 9049.
[6] (a) Levin, D. H.; Racker, E. *J. Biol. Chem.* **1959**, *234*, 2532-2539. (b) Unger, F. M. *Adv. Carbohydr. Chem. Biochem.* **1981**, *38*, 323-388.
[7] Nadano, D.; Iwasaki, M.; Endo, S.; Kitajima, K.; Inoue, S.; Inoue, Y. *J. Biol. Chem.* **1986**, *38,* 323.
[8] Schreiner, E.; Zbiral, E. *Liebigs Ann.Chem.* **1990**, 581.
[9] Inoue, S.; Lin, S. -L.; Chang, T.; Wu, S. -H.; Yao, C. -W.; Chu, T. -Y.; Troy, F. A.; Inoue, Y. *J. Biol. Chem.* **1998**, *273*, 27199–27204.



Reagents and conditions: (a) Lit 10; (b) 3-bromopropyne, DMF-Et_2O, Zn, 83%; (c) MOMCl, iPr_2NEt, 0 °C to rt, 88%; (d) NBS, $AgNO_3$, acetone, rt, 86%; (e) $KMnO_4$, $NaHCO_3$, $MgSO_4$, MeOH/H_2O (1:1), 0 °C, 87%; (f) conc. HCl, anhydrous MeOH, rt, 2 days, then Ac_2O, Py., DMAP, CH_2Cl_2, rt, 75% (two steps) (anomeric mixture about 4:1).

Scheme A-2[10]



(a) (i) Conc. H_2SO_4, acetone, 82%; (ii) $LiAlH_4$, THF, 92%; (b) TBSCl, DMF, Im., rt, 96%; (c) MOMCl, *i*-Pr_2NEr, CH_2Cl_2, rt, 92%; (d) *n*-Bu_4NF,THF, 93%; (e) (i) oxalyl chloride, DMSO, Et_3N; (ii) 3-bromopropyne, Zn, DMF-Et_2O, 77%; (f) TBSCl, DMF, Im., rt, 84%; (g) NBS, $AgNO_3$, acetone, 87%; (h) $KMnO_4$, $NaHCO_3$, $MgSO_4$, CH_3OH/H_2O (1:1), 0 ºC, 79%; (i) conc. HCl, anhydrous CH_3OH, r.t., then Ac_2O, Py., DMAP, CH_2Cl_2, rt, 78% (two steps)

Scheme A-3 Total synthesis of KDN

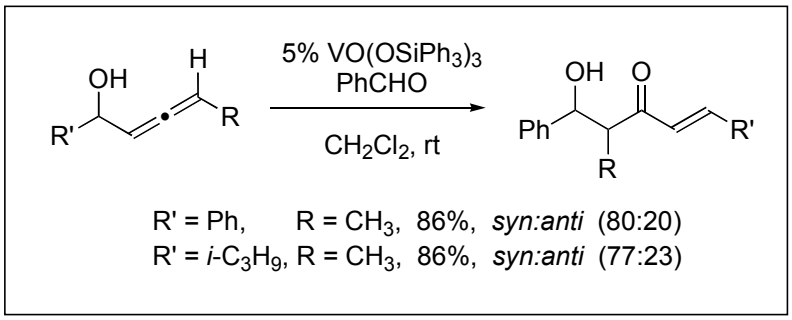
[10] Regeling, H.; de Rouville, E.; Chittenden, G. J. F. *Recl. Trav. Chim. Pays-Bas* **1987**, *106*, 461–464.

A.3 Applications of Allenic Alcohols

Allenes are a class of compounds with unique reactivity due to the existence of two orthogonal π-bonds, and they also been found to be very useful intermediates in organic synthesis.[11,12]

A.3.1 Addition of Allenic Alcohols and Aldehydes

Recently, Trost and co-workers reported that addition of allenic alcohols and aldehydes gave aldol-type adducts formally derived from an α,β-unsaturated ketone and an aldehyde, which is a particularly versatile juxtaposition of functionalities (Scheme A-4).[13]



Scheme A-4 Addition of allenic alcohols and aldehydes

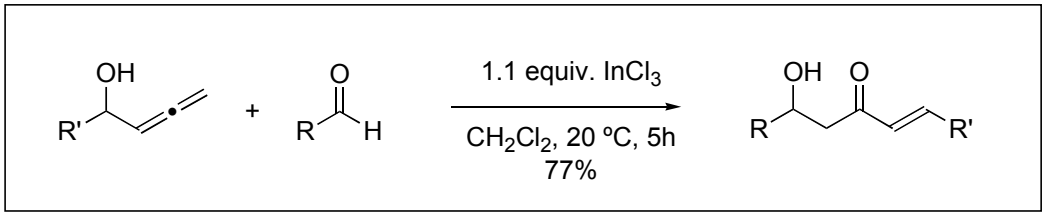
[11] (a) Schuster, H. F.; Coppola, G. M. *Allenes in Organic Synthesis;* John Wiley & Son: New York, **1988**. (b) *The Chemistry of Ketenes, Allens, and Related Compounds;* Patai, S. Ed.; John Wiley & Son: New York, **1980**; Part 1.

[12] (a) Walkup, R. D.; Kim, S. W.; Wagy, S. D. *J. Org. Chem.* **1993**, *58,* 6484. (b) Fox, D. N. A.; Lathbury, D.; Mahon, M. F.; Malloy, K. C.; Gallagher, T. *J. Am. Chem. Soc.* **1991**, *113,* 2652. (c) Kimura, M.; Fugami, K.; Tanaka, S.; Tamaru, Y. *J. Org. Chem.* **1992**, *57,* 6377. (d) Yamamoto, Y. Y.; Al-Masum, M.; Asao, N. *J. Am. Chem. Soc.* **1994**, *116,* 6019. (e) Trost, B. M.; Gerusz, V. *J. Am. Chem. Soc.* **1995**, *117.* 5156. (f) Wei, L. -L.; Mulder, J. A.; Xiong, H.; Zificsak, C. A.; Douglas, C. J.; Hsung, R. P. *Tetrahedron* **2001**, *57*, 459.

[13] Trost, B. M.; Jonasson, C.; Wuchrer, M. *J. Am. Chem. Soc.* **2001**, *123,* 12736.

This strategy provided a new synthetic method for the synthesis of unusual aldol-type products consisting of both an α,β-unsaturated ketone and a β-hydroxyketone, which cannot be easily obtained by other methods in an atom economical fashion.

The use of $InCl_3$ to promote reaction of allenic carbinols and aldehydes have been studied by Yu and co-workers. From their study, they found that in the presence of equimolar $InCl_3$ (1.1 eq), β-hydroxy enones was the major product in CH_2Cl_2 (Scheme A-5).[14]

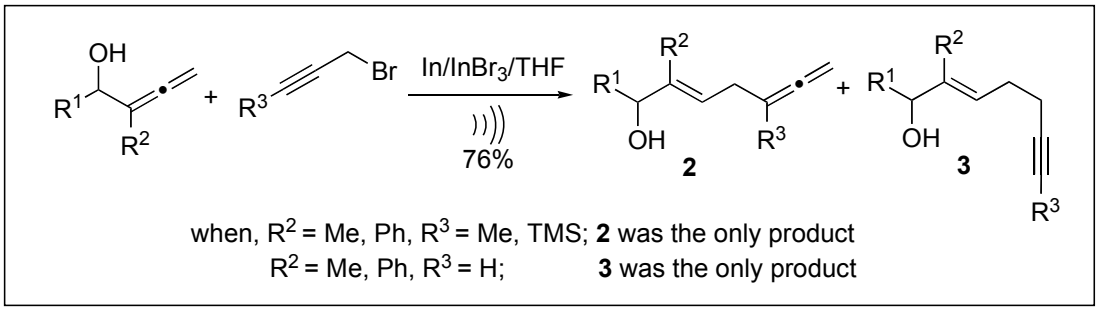


Scheme A-5 $InCl_3$ catalyze addition of allenic alcohols and aldehydes

A.3.2 Addition of Allenic Alcohols and Alkyl Halides

Recently, Miao and Chan found that indium-mediated reaction of propargyl bromide and allenic carbinol in the presence of indium tribromide gave *E*-1-substituted-2,5-dimethyl heptarien-1-ol (**2**) in moderate to good yield under ultrasonic irradiation (Scheme A-6). It is interesting to note that with parent propargyl bromide (R^3 = H) the reaction showed a different regioselectivity giving the homopropargyl carbometallation adduct **3** (Scheme A-6).[15]

[14] Yu, C. -M.; Kim, Y. -M.; Kim, J. -M. *Synlett.* **2003**, *10*, 1518.
[15] Miao, W.; Chan, T. -H. *Synthesis* **2003**, *5,* 785.



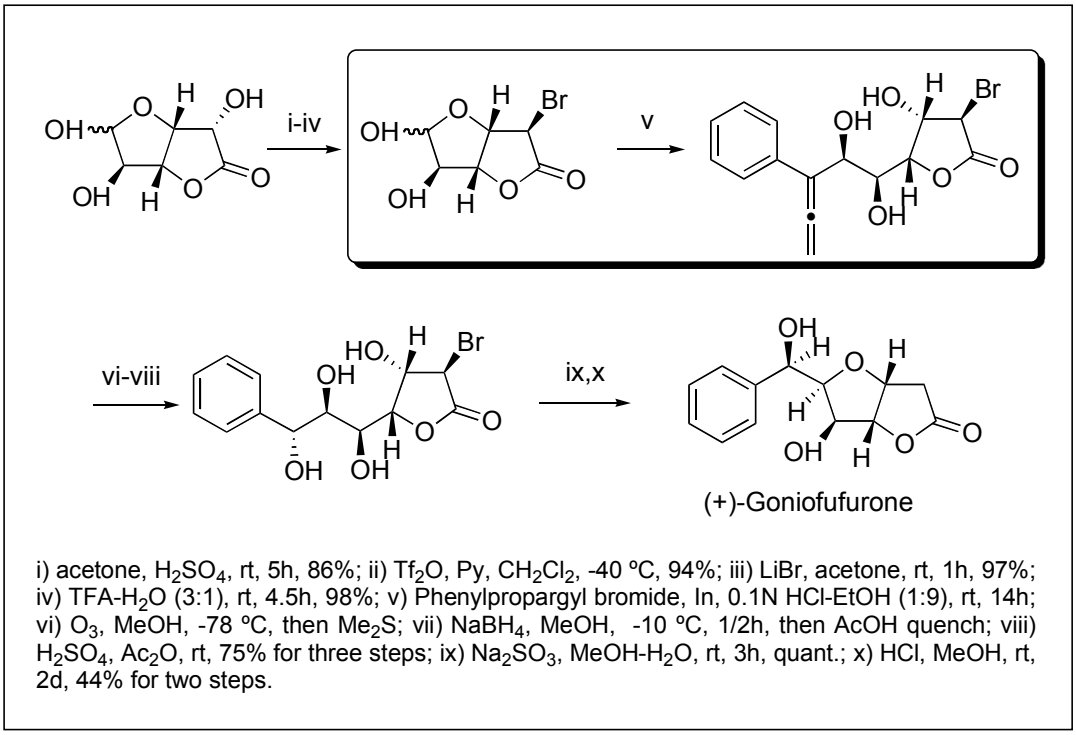
Scheme A-6 Indium-mediated reaction of propargyl bromide and allenic carbinol

A.3.3 Allenic alcohols as intermediates in organic synthesis

In addition, allenic alcohols were also found to be important building blocks in the synthesis of biological active natural products. Two natural styryl lactone, (+)-goniofufurone and (±)-9-deoxygoniopypyrone were derived from allenic alcohols.

(+)-Goniofufurone is one of a key component isolated from the Asia trees of the genus *Goniothalamus*, which found to possess moderate to significant cytotoxicities against several human tumors.[16] By using the indium-mediated allenylation of hemiacetal followed by functional group transformation, Li and co-workers completed the synthesis of the (+)-goniofufurone (Scheme A-7).[17]

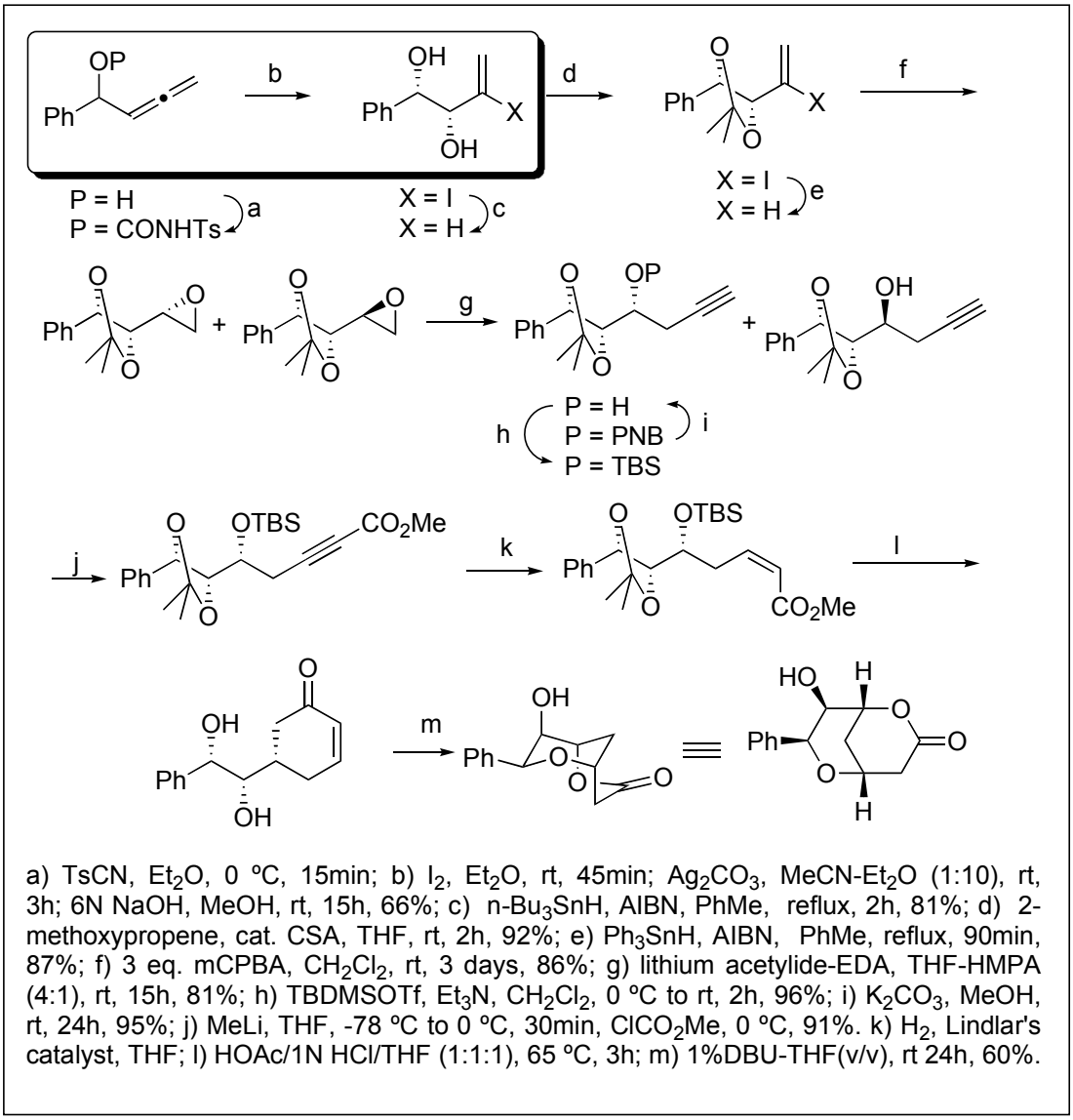
[16] Fang, X. -P.; Anderson, J. E.; Chang, C. -J.; Fanwick, P. E.; McLaughlin, J. L. *J. Chem. Soc., Perkin Trans, 1,* **1990**, 1655.
[17] (a) Yi, X, -H.; Meng, Y.; Li, C. -J. *Chem. Common.* **1998**, 449. (b) Yi, X, -H.; Meng, Y.; Hua, X. G.; Li, C. -J. *J. Org. Chem.* **1998**, *63,* 7472.



Scheme A-7 Total synthesis of (+)-Goniofufurone

Another styryl lactone, (±)-9-Deoxygoniopypyrone, with cytotoxic activity isolated from the stem bark of *Goniothalamus* had also been synthesized using α-allenic alcohol as starting material. The total synthesis of (±)-9-Deoxygoniopypyrone was successfully accomplished in thirteen steps. The relative configuration of the three contiguous asymmetric centers were established by the highly diastereoselective formation of the *syn*-vicinal diol *via* the iodo-cyclofunctionalization reaction of the allenic carbamate, and the epoxidation of the olefinic acetonide (Scheme A-8).[18]

[18] Friesen, R. W.; Bissada, S. *Tetrahedron Lett.* **1994**, *35,* 5618.



a) TsCN, Et_2O, 0 ºC, 15min; b) I_2, Et_2O, rt, 45min; Ag_2CO_3, MeCN-Et_2O (1:10), rt, 3h; 6N NaOH, MeOH, rt, 15h, 66%; c) n-Bu_3SnH, AIBN, PhMe, reflux, 2h, 81%; d) 2-methoxypropene, cat. CSA, THF, rt, 2h, 92%; e) Ph_3SnH, AIBN, PhMe, reflux, 90min, 87%; f) 3 eq. mCPBA, CH_2Cl_2, rt, 3 days, 86%; g) lithium acetylide-EDA, THF-HMPA (4:1), rt, 15h, 81%; h) TBDMSOTf, Et_3N, CH_2Cl_2, 0 ºC to rt, 2h, 96%; i) K_2CO_3, MeOH, rt, 24h, 95%; j) MeLi, THF, -78 ºC to 0 ºC, 30min, $ClCO_2Me$, 0 ºC, 91%. k) H_2, Lindlar's catalyst, THF; l) HOAc/1N HCl/THF (1:1:1), 65 ºC, 3h; m) 1%DBU-THF(v/v), rt 24h, 60%.

Scheme A-8 Total synthesis of (±)-9-Deoxygoniopypyrone

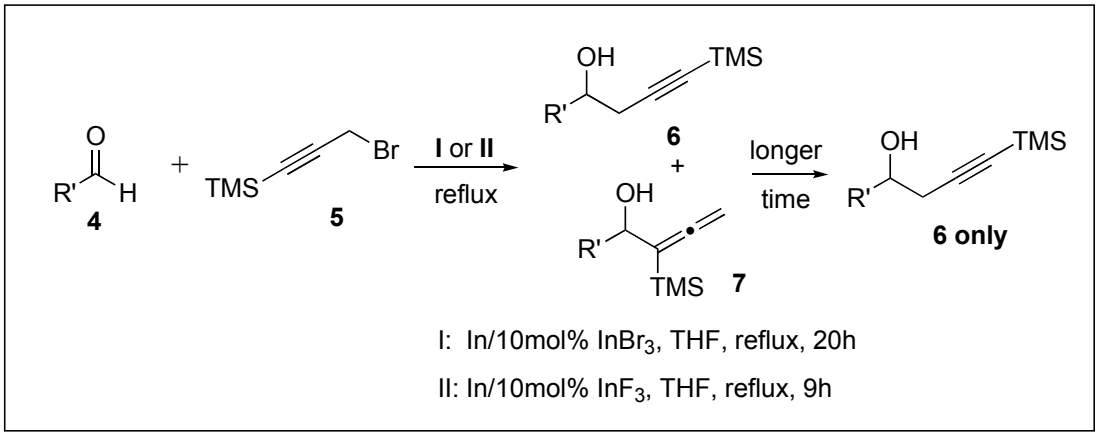
Accordingly, there has been much interest in the development of new methods for the synthesis of these classes of compounds. Among the methods available, the metal-mediated propargylation/allenylation of carbonyl compounds is the most common approach.[19] However, these methods are plagued with problems of poor regioselectivities and enantioselectivities. Therefore, a general and efficient method to

[19] (a) Lin, M. -J.; Loh, T. -P. *J. Am. Chem. Soc.* **2003,** *125,* 13042. (b) Loh, T. -P; Lin, M. -J.; Tan, K. L. *Tetrahedron Lett.* **2003,** *44,* 507. (c) Marshall, J. A. *Chem. Rev.* **2000**, *100,* 3163. (d) Daniels, R. G.; Paquette, L. A. *Tetrahedron Lett.* **1981**, *22*, 1579.

obtain this class of compounds is still highly desirable. Here, we report an efficient method for the propargylic transfer to carbonyl compounds based on an unusual oxonium-Claisen rearrangement of 2-trialkylsilyl allenic alcohols with aldehydes.

A.4 Results and Discussion

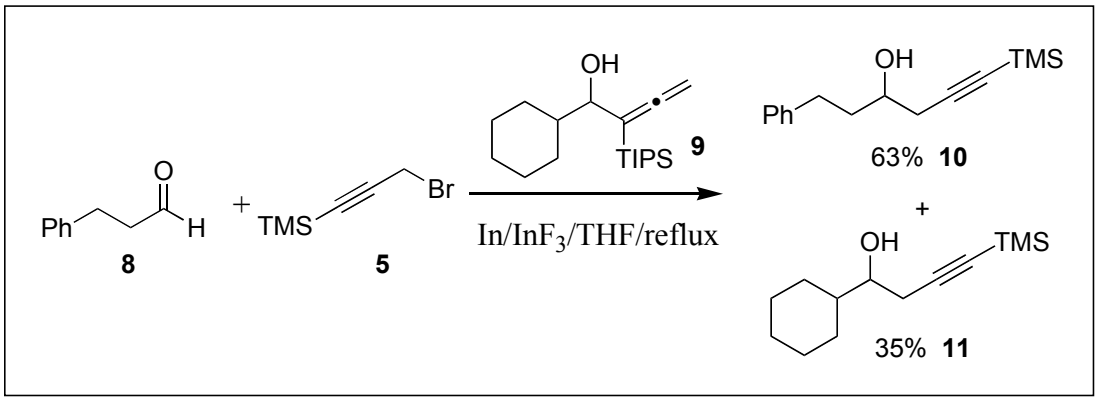
In the previous studies of homopropargylation in the presence of InF_3 or $InBr_3$,[20] a mixture of homopropargylic **6** and allenic alcohols **7** is formed initially with the homopropargylic alcohol **6** observed as the major product. Refluxing the reaction longer afforded only the homopropargylic alcohols **6** (Scheme A-9).



Scheme A-9

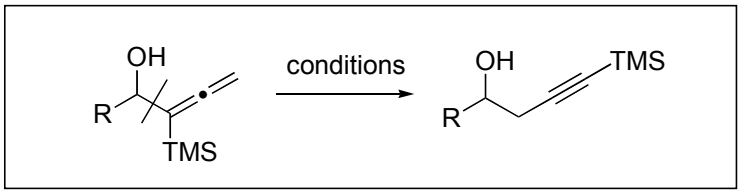
In addition, introducing α-triisopropylsilyl cyclohexyl allenic alcohol (**9**) to the indium-mediated reaction of propargyl bromide **5** and aldehyde **8** afforded the cross-over product **11** in addition to the indium-mediated coupling product **10** (Scheme A-10).

[20] Lin Manjing's PhD Thesis, **2003**.



Scheme A-10 Cross-over reaction

Although the reaction mechanism is not clear, the observation described above indicated that trimethylsilyl allenic alcohol maybe undergoing a retro cleavage followed by a rearrangement in the homoproparpylation reaction to afford trimethylsilyl homopropargylic alcohols (Scheme A-11). Therefore, it is interesting to find out further how this reaction goes.



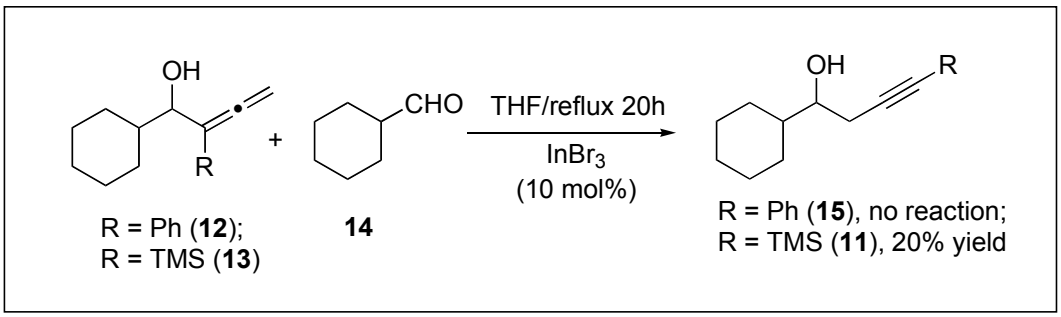
Scheme A-11 Rearrangement

Recently, it has been demonstrated by Nokami and co-workers that the γ-allyl adduct underwent a retroene reaction, *via* a hemiacetal, derived from an aldehyde and the allenic alcohol, followed by a six-membered cyclic transition state 2-oxonia [3,3]-

sigmatropic rearrangement in the presence of Lewis acid to give the corresponding α-adduct.[21]

Therefore, it is of great interest to find out whether the allenic alcohols can be rearranged to the corresponding homopropargylic alcohols *via* a similar transition state by an acid catalyst or otherwise.

In our initial investigations, THF solutions of two 2-substituted allenic alcohols (**12**,**13**) in the presence of 10 mol% indium tribromide ($InBr_3$) under reflux condition were carried out to investigate whether allenic alcohols can rearrange to afford homopropargylic alcohols (Scheme A-12).



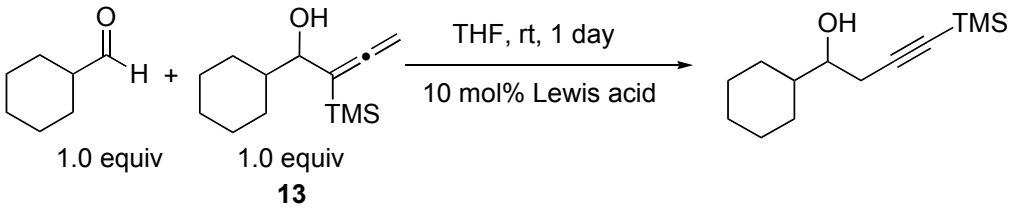
Scheme A-12

Unfortunately, no desired corresponding homopropargylic alcohols were obtained when 2-phenyl-substituted α-allenic alcohols **12** were subjected to various aldehydes under these conditions. To our surprise, when one equivalent of the corresponding aldehyde[21] was introduced to 2-trimethylsilyl allenic alcohol **13** in the presence of $InBr_3$ (10 mol%), the desired homopropargylic alcohol **11** was obtained in

[21] (a) Nokami, J.; Anthony, L.; Sumida, S. *Chem. Eur. J.* **2000**, *6*, 2909. (b) Tan, K. -T.; Chng, S. -S.; Cheng, H. -S.; Loh, T. -P. *J. Am. Chem. Soc.* **2003**, *125*, 2958. (c) Ripoll, J. L.; Vallée, Y. *Synthesis* **1993**, 659.

20% yield together with the recovery of 30% of the starting allenic alcohol **13**. With this promising result, the α-trimethylsilyl cyclohexyl allenic alcohol **13** in the presence of the corresponding aldehyde, were subjected with various Lewis acids. The results are shown in Table A-1.

Table A-1 Effect of Lewis Acids[a]



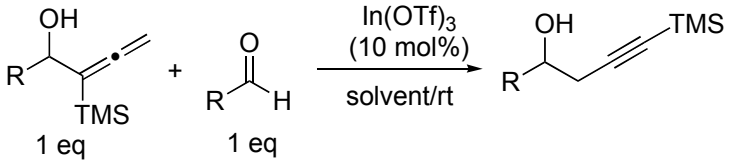
Entry	Lewis Acid	Yield[b] %
1	$InCl_3$	-
2	$Cu(OTf)_2$	-
3	InBr	5
4	$InBr_3$	20[c]
5	$Sc(OTf)_3$	26
6	$In(OTf)_3$	51

[a] All reactions were carried out on 0.5 mmol scale at room temperature in THF (2 mL). [b] Isolated yield. [c] Recovered back 30% of the starting material.

It is interesting to note that the use of indium triflates with more Lewis acid characteristic afforded the desired homopropargylic alcohols in moderate yield (entry 6). Next, different α-trimethylsilyl allenic alcohols were subjected to the rearrangement using this condition (Table A-2). Compared to other α-trimethylsilyl allenic alcohols, we found that cyclohexyl allenic alcohol afforded the crossover

product in higher yield, probably due to the more sterically hindered cyclohexyl allenic alcohol.

Table A-2 Rearrangement of Various Allenic Alcohols[a]

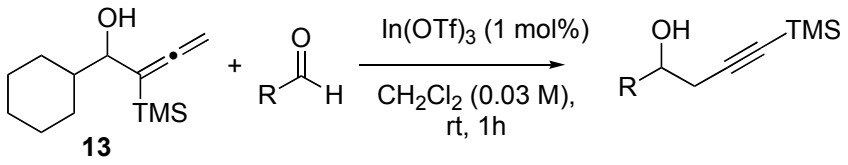


Entry	R	Conditions	Yield[b] %
1	$PhCH_2CH_2$	THF / 24h	30
2	C_8H_{17}	THF / 24h	45
3	Ph	THF / 24h	50
4	*c*-C_6H_{11}	THF / 24h	51
5	*c*-C_6H_{11}	CH_2Cl_2 / 1h	89

[a] All reactions were carried out on 0.5 mmol scale at room temperature in solvent (2 mL). [b] Isolated yield.

Next, using these optimized conditions, the cross-over reactions of α-trimethylsilyl cyclohexyl allenic alcohol and various aldehydes were carried out in CH_2Cl_2 in the presence of 1 mol% of $In(OTf)_3$. The results are shown in Table A-3. In this reaction, complete conversions of crossover products were obtained. The selectivity between cross-over and self-rearranged product could be improved when the reaction was carried out using 2 to 4 equivalents of aldehyde in the presence of 1 mol% of indium triflate. After the reaction, the excess aldehyde can be recovered in quantitative yield through flash column chromatography. The isolated yields were good, and only small amounts of the self-rearranged products were detected.

Table A-3 Crossover Reactions of Allenic Alcohols and Aldehydes in CH_2Cl_2 with $In(OTf)_3$[a]

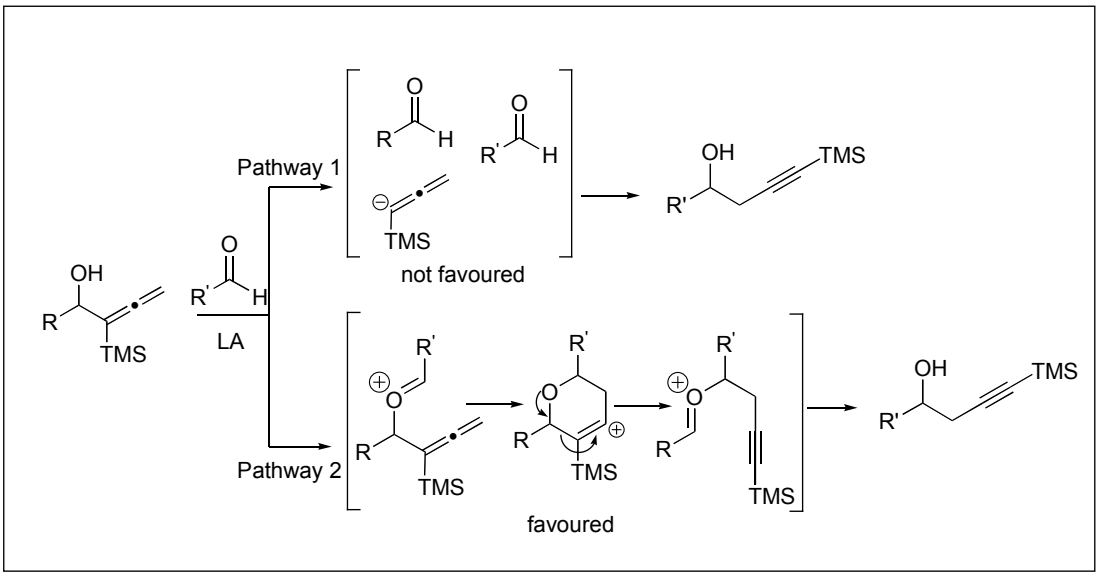


Entry	R	Yield[b] %
1	*c*-C_6H_{11}-	98
2	$PhCH_2CH_2$-	79
3	$BnO(CH_2)_3$-	78
4	C_8H_{17} -	77
5	$C_2H_5CH=CHC_2H_4$- (*cis*)	77
6	$BnO(CH_2)_2$-	73[c]
7	$(CH_3)_2CHCH_2$-	73
8	C_5H_{11} -	71
9	$CH_2=CHCH_2O(CH_2)_4$ -	70

[a] Unless otherwise noted, all reactions were carried out on 0.2 mmol scale in CH_2Cl_2 (0.03M) for 1h at room temperature. [b] Isolated yield. [c] 100% recovery of the excess aldehyde.

Two possible reaction pathways (Scheme A-13) can be envisaged to occur during this rearrangement. Pathway 1 involves the reaction of an intermolecular allenic anion (generated in the reaction) to the aldehyde. On the other hand, pathway 2 involves an unprecedented oxonium [3, 3]-sigmatropic rearrangement of the allenic alcohol in the presence of aldehyde and Lewis acid catalyst. In order to further understand the mechanism involved in this reaction, we carried out stereochemical

studies using enantiomerically enriched allenic alcohol **13** (92% *ee*).[22] The results are summarized in Table A-4.



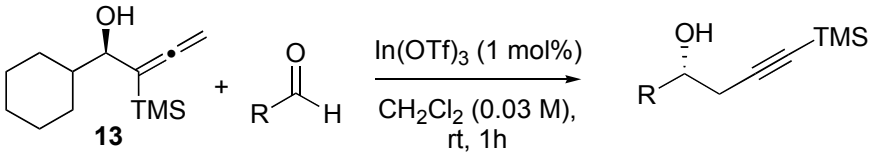
Scheme A-13 Proposed mechanism for rearrangement/cross-over of allenic alcohol

The crossover experiments were further performed with selected aldehydes under the same conditions. In all cases, the products were obtained in high enantioselectivities (88% to 97% *ee*, corrected based on 92% *ee* of the starting material). Furthermore, the products were obtained in the opposite configuration as compared to the starting material. With these results, we believe that this allenic alcohol undergoes an 2-oxonia [3,3]-sigmatropic rearrangement in the presence of aldehyde to give the homopropargylic adduct. The requirement of the silicon substituent at the 2-position of the allenic alcohols was probably due to the more stepwise nature of this reaction where the silicon stabilized the β-carbocation. It is

[22] It was obtained by chiral resolution with *S*-(+)-α-acetoxyphenylacetic acid followed by hydrolysis. Enantiomeric excess for (-)-1-cyclohexyl-2-trimethylsilanyl-buta-2,3-dien-1-ol was 92 % *ee*. Whitesell, J.K.; Reynolds, D. *J. Org. Chem.* **1983**, *48*, 3548.

also possible that the rearrangement could be fully concerted where the silicon group stabilizes the transition state without a vinyl cation intermediate.

Table A-4 Rearrangement Using Optically Active Allenic Alcohol **13**[23,24]



Entry	R	% *ee*[a] (%)[e]	$[\alpha]_D^{25}$, $CHCl_3$	confign
1	$PhCH_2CH_2$	85[b] (92)	-17.7 (*c* 1.0)	*R*[c]
2	Ph	89[b] (97)	+43.6 (*c* 0.5)	*R*[d]
3	$BnO\text{-}C_2H_4$	81[b] (88)	+13 (*c* 0.05)	*R*[c]

[a] Enantiomeric excess was determined by chiral HPLC. [b] determine from (*R*)-1-cyclohexyl-2-trimethylsilanyl-buta-2,3-dien-1-ol with 92% *ee*. [c] predicted based on d. [d] based on ref. 24. [e] corrected value.

A.5 Conclusion

In conclusion, a new and efficient method to obtain the homopropargylic alcohols *via* the homopropargylic transfer from the allenic alcohol to various aldehydes in the presence of Lewis acid catalysis has been accomplished.[25] This represents the first hypothesized and tested oxonium [3,3]-sigmatropic rearrangement of an allenic alcohol to the homopropargylic alcohols in the presence of aldehydes and Lewis acid. The followings are the characteristics of this method: (1) This reaction works with a wide variety of aldehydes, affording a wide variety of

[23] Compain, P.; Gorè, J.; Vatèle, J. M. *Tetrahedron* **1996**, *52*, 10405.
[24] Brown, H. C.; Khire, U. R.; Narla, G. *J. Org. Chem*. **1995**, *60*, 8130.
[25] Lee, K. -C.; Lin, M. -J.; Loh, T. -P. *Chem. Commun*., **2004**, 2456-2457.

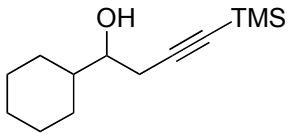
homopropargylic alcohols in good to excellent yields. (2) Only 1 mol% of the Lewis acid catalyst is required to catalyze the reaction and the excess aldehyde used in the reaction can be recovered in quantitative yields. (3) The reaction has also been shown to proceed with high enantioselectivities when optically active allenic alcohol was used as the starting material. (4) Silicon seems to play an important role in this type of rearrangement.

A.6 Experimental

Crossover Reactions of Allenic Alcohols and Aldehydes in CH_2Cl_2 with $In(OTf)_3$; General Procedure:

The mixture of cyclohexanecarboxyldehyde (89 mg, 0.8 mmol, 4 equiv) and 1-cyclohexyl-2-trimethylsilanyl-buta-2,3-dien-1-ol (45 mg, 0.2 mmol, 1 equiv) was added to a solution of indium triflate (1 mg, 0.002 mmol, 0.01 equiv) in 6 mL dried CH_2Cl_2 at room temperature under an atmosphere of dry nitrogen. The mixture was stirred for 1 hour and finally quenched with saturated sodium bicarbonate. Purification through flash silica gel column chromatography provides 44.1 mg (98% yield) of 1-cyclohexyl-4-trimenthylsilanyl-but-3-yn-ol as a colourless oil.

1-Cyclohexyl-4-trimenthylsilanyl-but-3-yn-ol (Table A-3, entry 1)



Yield%: 98%

R_f 0.67 (hexane : ethyl acetate 4:1)

^{1}H NMR: (300 MHz, $CDCl_3$)

δ 3.46-3.41 (1H, m, -C**H**OH), 2.43 (1H, dd, *J* = 16.71, 3.60 Hz, -C≡CC**H**H), 2.32 (1H, dd, *J* = 16.71, 7.65 Hz, -C≡CCH**H**), 2.12 (1H, brs, -CHO**H**), 1.86-0.96 (11H, m, *c*-$C_6\mathbf{H}_{11}$), 0.11 (9H, s, -Si($C\mathbf{H}_3$)$_3$) ppm

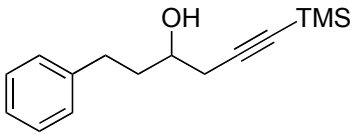
^{13}C NMR: (125 MHz, $CDCl_3$)

δ 103.7 (-**C**≡CSi), 87.3 (-C≡**C**Si), 73.8 (-**C**HOH), 42.6 (-**C**HCHOH), 28.9, 28.1, 26.3, 26.1, 26.0, 25.9 (-$\mathbf{C}H_2$), -0.01 (-Si($\mathbf{C}H_3$)$_3$) ppm

FTIR: 3402, 2928, 2851, 2663, 2174, 1713, 1450, 1422 cm^{-1}

EIHRMS: Calcd for $C_{13}H_{24}OSi$: 224.1596, found : 224.1594.

1-Phenyl-6-trimethylsilanyl-hex-5-yn-3-ol (Table A-3, entry 2)



Yield%: 79%

R_f 0.54 (hexane : ethyl acetate 4:1)

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.31-7.26 (2H, m, -Ph-**H**), 7.22-7.18 (3H, m, -Ph-**H**), 3.76 (1H, tt, *J* = 6.45, 5.55 Hz, -C**H**OH), 2.81 (1H, dt, *J* = 13.90, 7.35 Hz, -PhC**H**H), 2.71 (1H, dt, *J* = 13.90, 8.35 Hz, -PhCH**H**), 2.48 (1H, dd, *J* = 16.65, 5.10 Hz, -C≡CC**H**H), 2.40 (1H, dd, *J* = 16.65, 6.95 Hz, -C≡CCH**H**), 2.09 (1H, brs, -CHO**H**), 1.86 (2H, td, *J* = 8.35, 6.00 Hz, -$PhCH_2C\mathbf{H}_2$), 0.17 (9H, s, -$Si(C\mathbf{H}_3)_3$) ppm

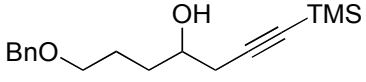
^{13}C NMR: (125 MHz, $CDCl_3$)

δ 141.7, 128.3, 125.8 (phenyl), 102.9 (-**C**≡CSi), 87.7 (-C≡**C**Si), 69.0 (-**C**HOH), 37.7 (-$\mathbf{C}H_2CHOH$), 31.8 (-Ph$\mathbf{C}H_2$), 28.9 (-$\mathbf{C}H_2C$≡C), 0.03 (-$Si(\mathbf{C}H_3)_3$) ppm

FTIR: 3434, 3020, 2961, 2170, 1718, 1492, 1454, 1411 cm^{-1}

EIHRMS: Calcd for $C_{15}H_{22}OSi$: 246.1440, found : 246.1396.

7-Benzyloxy-1-trimethylsilanyl-hept-1-yn-4-ol (Table A-3, entry 3)



Yield%: 78%

R_f 0.40 (hexane : ethyl acetate 4:1)

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.19-7.29 (5H, m, -Ph-**H**), 4.44 (2H, s, -OC**H**$_2$Ph), 3.70-3.66 (1H, m, -C**H**OH), 3.45 (2H, t, *J* = 6.00 Hz, BnOC**H**$_2$-), 2.60 (1H, brs, -CHO**H**), 2.36 (1H, dd, *J* = 16.65, 5.55 Hz, -C≡CC**H**H), 2.32 (1H, dd, *J* = 16.65, 6.50 Hz, -C≡CCH**H**), 1.73-1.47 (4H, m, -(C**H**$_2$)$_2$CH$_2$OBn), 0.09 (9H, s, -Si(C**H**$_3$)$_3$) ppm

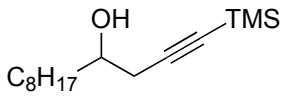
^{13}C NMR: (125 MHz, CDCl$_3$)

δ 138.1, 128.3, 127.6, 127.5 (Phenyl), 103.4 (-**C**≡CSi), 87.2 (-C≡**C**Si), 72.9 (-O**C**H$_2$-), 70.2 (-O**C**H$_2$-), 69.7 (-**C**HOH), 33.3 (-**C**H$_2$CHOH), 28.7 (-**C**H$_2$C≡C-), 26.0 (BnOCH$_2$**C**H$_2$-), 0.04 (-Si(**C**H$_3$)$_3$) ppm

FTIR: 3409, 3088, 3064, 3031, 2957, 2929, 2902, 2859, 2174, 1605, 1454 cm^{-1}

EIHRMS: Calcd for $C_{17}H_{26}O_2Si$: 290.1702, found : 290.1701.

1-Trimethylsilanyl-dodec-1-yn-4-ol (Table A-3, entry 4)



Yield%: 77%

R$_f$ 0.68 (hexane : ethyl acetate 4:1)

^{1}H NMR: (300 MHz, CDCl$_3$)

δ 3.71 (1H, tt, *J* = 6.50, 5.55 Hz, -C**H**OH), 2.45 (1H, dd, *J* = 16.71, 4.89 Hz, -C≡CC**H**H), 2.33 (1H, dd, *J* = 16.71, 6.96 Hz, -C≡CCH**H**), 1.96 (1H, brs, -CHO**H**), 1.48-1.52 (2H, m, -C**H**$_2$CHOH), 1.27 (12H, m, -(C**H**$_2$)$_6$), 0.87 (3H, t, *J* = 5.90 Hz, C**H**$_3$), 0.15 (9H, s, -Si(C**H**$_3$)$_3$) ppm

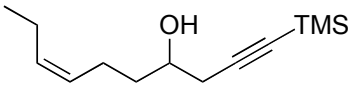
^{13}C NMR: (75 MHz, CDCl$_3$)

δ 103.4 (-**C**≡CSi), 86.9 (-C≡**C**Si), 70.0 (-**C**HOH), 36.2 (-**C**H$_2$CHOH), 31.9, 29.5, 29.3, 28.9, 25.6, 22.7 (-(**C**H$_2$)$_6$CH$_3$), 14.1 (-**C**H$_3$), 0.07 (-Si(**C**H$_3$)$_3$) ppm

FTIR: 3365, 2957, 2926, 2855, 2176, 1465 cm^{-1}

EIHRMS: Calcd for $C_{15}H_{30}OSi$: 254.2066, found : 254.2067.

1-trimethylsilanyl-dec-7-en-1-yn-4-ol (Table A-3, entry 5)



Yield%: 77%

R_f 0.64 (hexane : ethyl acetate 4:1)

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 5.39 (1H, m, **H**C=CH), 5.32 (1H, m, HC=C**H**), 3.74 (1H, tt, *J* = 6.00, 5.55 Hz, C**H**OH), 2.45 (1H, dd, *J* = 16.65, 4.65 Hz, -C≡CC**H**H), 2.35 (1H, dd, *J* = 16.65, 6.50 Hz, -C≡CCH**H**), 2.19-2.10 (2H, m, -C=CC**H$_2$**CH_3), 2.08-2.02 (2H, m, -C=CC**H$_2$**CH_2), 2.00 (1H, brs, -CHO**H**), 1.58 (2H, td, *J* = 7.62, 6.50 Hz, C**H$_2$**CHOH), 0.96 (3H, t, *J* = 7.65 Hz, -CH_2C**H$_3$**), 0.15 (9H, s, -Si(C**H**$_3$)$_3$) ppm

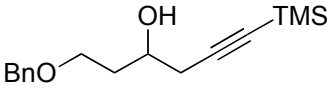
^{13}C NMR: (125 MHz, $CDCl_3$)

δ 132.4 (-H**C**=CH-), 128.1(-HC=**C**H-), 103.1 (-**C**≡CSi-), 87.6 (-C≡**C**Si-), 69.4 (-**C**HOH), 36.1 (-**C**H_2), 28.8 (-**C**H_2C≡C-), 23.3 (-**C**H_2), 20.4 (-**C**H_2), 14.2 (-CH_2**C**H_3), 0.03 (-Si(**C**H_3)$_3$) ppm

FTIR: 3392, 3007, 2962, 2933, 2875, 2856, 2176, 1654, 1453 cm^{-1}

EIHRMS: Calcd for $C_{13}H_{24}OSi$: 224.1596, found : 246.1600.

1-Benzyloxy-6-trimethylsilanyl-hex-5-yn-3-ol (Table A-3, entry 6)



Yield%: 73%

R_f 0.46 (hexane : ethyl acetate 4:1)

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.30-7.27 (5H, m, -Ph-**H**), 4.52 (2H, s, -PhC**H**$_2$O), 3.96 (1H, ttd, *J* = 6.50, 6.45, 2.75 Hz, -C**H**OH), 3.73 (1H, ddd, *J* = 9.49, 7.88, 4.65 Hz, BnOC**H**H-), 3.65 (1H, ddd, *J* = 10.88, 7.65, 4.65 Hz, BnOCH**H**-), 2.46 (1H, dd, *J* = 17.10, 6.05 Hz, C≡CC**H**H), 2.41 (1H, dd, *J* = 17.10, 6.45 Hz, -C≡CCH**H**), 1.92 (1H, dddd, *J* = 14.32, 6.48, 4.65, 3.25 Hz, BnOCH$_2$C**H**H-), 1.86-1.79 (1H, m, BnOCH$_2$CH**H**-), 0.15 (9H, s, -Si(C**H**$_3$)$_3$) ppm

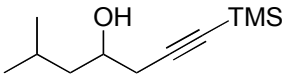
^{13}C NMR: (125 MHz, $CDCl_3$)

δ 137.8, 128.4, 127.7, 127.6 (Phenyl), 103.3 (-**C**≡CSi-), 87.0 (-C≡**C**Si-), 73.2 (-O**C**H$_2$-), 69.3 (-**C**HOH), 68.4 (-O**C**H$_2$-), 35.3 (-**C**H$_2$CHOH), 28.5 (-**C**H$_2$C≡C-), 0.04 (-Si(**C**H$_3$)$_3$) ppm

FTIR: 3430, 3089, 3065, 3032, 2958, 2926, 2900, 2863, 2175, 1632, 1454 cm^{-1}

EIHRMS: Calcd for $C_{16}H_{23}O_2Si$ (M^+) : 275.1473, found : 275.1466.

6-methyl-1-trimethylsilanyl-hept-1-yn-4-ol (Table A-3, entry 7)



Yield%: 73%

R$_f$ 0.61 (hexane : ethyl acetate 4:1)

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 3.80 (1H, m, -C**H**OH), 2.43 (1H, dd, *J* = 16.62, 4.65 Hz, -C≡CC**H**H), 2.32 (1H, dd, *J* = 16.62, 6.95 Hz, -C≡CCH**H**), 1.77 (1H, m, -C**H**(CH$_3$)$_2$), 1.45 (1H, ddd, *J* = 14.20, 8.88, 8.66 Hz, (CH$_3$)$_2$CHC**H**H-), 1.29 (1H, ddd, *J* = 14.20, 8.88, 8.55 Hz, (CH$_3$)$_2$CHCH**H**-), 0.91 (6H, q, *J* = 3.45 Hz, -CH(C**H**$_3$)$_2$), 0.15 (9H, s, -Si(C**H**$_3$)$_3$) ppm

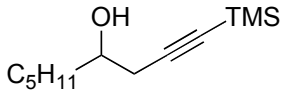
^{13}C NMR: (125 MHz, $CDCl_3$)

δ 103.3 (-**C**≡CSi-), 87.6 (-C≡**C**Si-), 68.0 (-**C**HOH), 45.4 ((CH$_3$)$_2$CH**C**H$_2$-), 29.3 (-**C**H$_2$C≡C-), 24.6 (-**C**H(CH$_3$)$_2$), 23.3, (-CH**C**H$_3$), 22.1 (-CH**C**H$_3$) 0.05 (-Si(**C**H$_3$)$_3$) ppm

FTIR: 3401, 2958, 2929, 2871, 2176, 1641, 1467 cm^{-1}

EIHRMS: Calcd for $C_{11}H_{22}OSi$: 198.1440, found : 198.1397.

1-Trimethylsilanyl-non-1-yn-4-ol (Table A-3, entry 8)



Yield: 71%.

R_f: 0.64 (Hexane : Ethyl Acetate = 4:1)

^{1}H NMR (500 MHz, $CDCl_3$):

δ 3.72 (1H, tt, *J* = 6.45, 5.55 Hz, -C**H**OH), 2.44 (1H, dd, *J* = 16.75, 4.60 Hz, -C≡CC**H**H), 2.44 (1H, dd, *J* = 16.75, 6.95 Hz, -C≡CCH**H**), 1.53-1.49 (2H, m, -C$\mathbf{H}_2$), 1.33-1.27 (6H, m, (-C$\mathbf{H}_2$)$_3$), 0.87 (3H, t, *J* = 6.95 Hz, -C$\mathbf{H}_3$), 0.15 (9H, s, -Si(C$\mathbf{H}_3$)$_3$) ppm

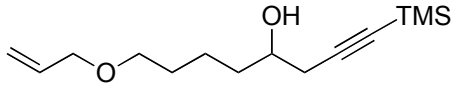
^{13}C NMR: (125 MHz, $CDCl_3$)

δ 103.3 (-**C**≡CSi-), 87.5 (-C≡**C**Si-), 69.9 (-**C**HOH), 36.2 (-**C**H_2CHOH), 31.7, 28.8, 25.2, 22.5 -(**C**H_2)$_4$$CH_3$), 13.9 (-($CH_2$)$_4$**C**$H_3$), 0.04 (-Si(**C**$H_3$)$_3$) ppm

FTIR: 3394, 2958, 2932, 2873, 2859, 2176, 1421 cm^{-1}

EIHRMS: Calcd for $C_{12}H_{24}OSi$: 212.1596, found : 212.1596.

8-Allyloxy-1-trimethylsilanyl-oct-1-yn-4-ol (Table A-3, entry 9)



Yield%: 70%

R_f 0.42 (hexane : ethyl acetate 4:1)

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 5.89 (1H, tdd, *J* = 11.47, 10.53, 5.55 Hz, -C**H**=CH_2), 5.25 (1H, ddt, *J* = 10.53, 3.25, 1.85 Hz, -CH=C**H**H), 5.15 (1H, ddt, *J* = 11.47, 3.00, 1.40 Hz, -CH=CH**H**), 3.95 (2H, dt, *J* = 6.00, 1.40 Hz, -CH_2=CHC**H**$_2$O), 3.72 (1H, quintet, *J* = 6.00 Hz, -C**H**OH), 3.42 (2H, t, *J* = 6.50 Hz, AllyOC**H**$_2$-), 2.44 (1H, dd, *J* = 16.62, 5.10 Hz, -C≡CC**H**H), 2.34 (1H, dd, *J* = 16.62, 6.95 Hz, -C≡CCH**H**), 2.07 (1H, brs, -CHO**H**), 1.37-1.66 (6H, m, AllyOCH_2(C**H**$_2$)$_3$-), 0.14 (9H, s, -Si(C**H**$_3$)$_3$) ppm

^{13}C NMR: (125 MHz, $CDCl_3$)

δ 134.9 (-**C**H=CH_2), 116.7 (-CH=**C**H$_2$), 103.2 (-**C**≡CSi-), 87.5 (-C≡**C**Si-), 71.8 (-O**C**H$_2$-), 70.1 (-O**C**H$_2$-), 69.7 (-**C**HOH), 35.9 (-**C**H$_2$CHOH), 29.5 (-CH_2-), 28.8 (-**C**H$_2$C≡C-), 22.2 (-**C**H$_2$-) 0.03 (-Si(**C**H$_3$)$_3$) ppm

FTIR: 3427, 3081, 2939, 2863, 2175, 1420 cm^{-1}

ESIHRMS: Calcd for $C_{14}H_{26}O_2SiNa$: 277.1600, found : 277.1599.

Chiral resolution of **13** was carried out with *S*-(+)-α-acetoxyphenylacetic acid followed by hydrolysis. For the standard procedure, refer to Whitesell, J.K.; Reynolds, D. *J. Org. Chem.* **1983**, *48*, 3548. (Note: the separation of the *S*-(+)-α-acetoxyphenylacetic-ester of **13** was done by silica gel column chromatography with Hexane:Acetone = 250:0.5 as mobile phase).

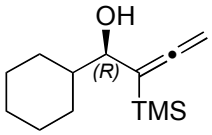
Enantiomeric excess for (-)-1-cyclohexyl-2-trimethylsilanyl-buta-2,3-dien-1-ol was 92 % by NMR (500 MHz, $CDCl_3$) analysis.

The configurations were determined based on literature:

Brown, H.C.; Khire, U.R.; Narla, G. *J. Org. Chem.* **1995**, *60*, 8130-8131.

Compain, P.; Gorè, J.; Vatèle, J.M. *Tetrahedron* **1996**, *52*(31), 10405-10416.

(*R*)-1-Cyclohexyl-2-trimethylsilanyl-buta-2,3-dien-1-ol (13)



Selectivity: 92 % *ee*

Opt. Rot.: $[\alpha]_D^{25}$ -16.95 (*c* = 7.8 in $CHCl_3$)

R_f 0.75 (hexane : ethyl acetate 4:1)

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 4.54 (1H, dd, *J* = 11.10, 2.3 Hz, -C=C=C**H**H), 4.50 (1H, dd, *J* = 11.10, 2.3 Hz, -C=C=CH**H**), 3.91 (1H, m, -C**H**OH), 1.85-0.96 (11H, m, *c*-C_6**H**$_{11}$), 0.14 (9H, s, -Si(C**H**$_3$)$_3$) ppm

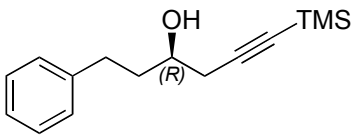
^{13}C NMR: (125 MHz, $CDCl_3$)

δ 207.5 (-C=**C**=CH_2), 99.5 (-**C**=C=CH_2), 75.1 (-**C**HOH), 71.5 (-C=C=**C**H_2), 43.6 (-**C**HCHOH), 30.4, 26.8, 26.4, 26.3, 26.0 (-**C**H_2-), -0.8 (-Si(**C**H_3)$_3$) ppm

FTIR: 3436, 2929, 2855, 1925, 1716, 1666, 1449 cm^{-1}

EIHRMS: Calcd for $C_{13}H_{24}OSi$: 224.1596, found : 224.1592.

(*R*)-Cyclohexyl-4-trimenthylsilanyl-but-3-yn-ol (Table A-4, entry 1)



Selectivity: 84 % *ee*

Opt. Rot.: $[\alpha]_D^{25}$ +15.8 (*c* = 0.9 in $CHCl_3$)

HPLC analysis employing a Daicel Chiracel OD column

(Hexane: *i*-propanol 99:1, 0.3 mL/min: t1 = 14.08, t2 = 19.72.

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.30-7.27 (2H, m, -Ph-**H**), 7.21-7.17 (3H, m, -Ph-**H**), 3.75 (1H, quintet, *J* = 6.00 Hz, -C**H**OH), 2.81 (1H, dt, *J* = 13.63, 7.85 Hz, -PhC**H**H), 2.70 (dt, *J* = 13.63, 8.35 Hz, 1H, -PhCH**H**), 2.48 (1H, dd, *J* = 16.65, 4.65 Hz, -C≡CC**H**H), 2.38 (1H, dd, *J* = 16.65, 6.05 Hz, -C≡CCH**H**), 1.98 (1H, brs, -CHO**H**), 1.85 (2H, td, *J* = 7.70, 6.50 Hz, -$PhCH_2C\mathbf{H}_2$), 0.16 (9H, s, -$Si(C\mathbf{H}_3)_3$) ppm

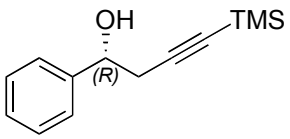
^{13}C NMR: (125 MHz, $CDCl_3$)

δ 141.7, 128.4, 125.8 (phenyl), 102.9 (-**C**≡CSi-), 87.8 (-C≡**C**Si-), 69.0 (-**C**HOH), 37.7 (-$\mathbf{C}H_2CHOH$), 31.8 (Ph$\mathbf{C}H_2$-), 28.9 (-$\mathbf{C}H_2C$≡C-), 0.05 (-$Si(\mathbf{C}H_3)_3$) ppm

FTIR: 3434, 3020, 2961, 2170, 1718, 1492, 1454, 1411 cm^{-1}

EIHRMS: Calcd for $C_{15}H_{22}OSi$: 246.1440, found : 246.1396.

(*R*)-Phenyl-4-trimethylsilanyl-but-3-yn-1-ol (Table A-4, entry 2)



Yield: 44%.

Selectivity: 89 % *ee*

Opt. Rot.: $[\alpha]_D^{25}$ = +43.6 (*c* = 0.5 in $CHCl_3$)

HPLC analysis employing a Daicel Chiracel OD-H column

(Hexane: *i*-propanol 99:1, 1 mL/min: t1 = 10.67, t2 = 14.00)

$\mathbf{R}_f$ 0.51 (Hexane : Ethyl Acetate = 4:1)

^{1}H NMR: (300 MHz, $CDCl_3$)

δ 7.38-7.26 (5H, m, -Ph-**H**), 4.84 (1H, t, *J* = 6.27 Hz, -PhC**H**OH), 2.65 (2H, d, *J* = 6.27 Hz, -$C\mathbf{H}_2$C≡CSi-), 2.45 (1H, brd, -CHO**H**), 0.17 (9H, s, -$Si(C\mathbf{H}_3)_3$) ppm

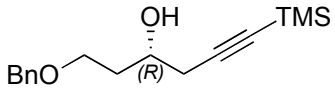
^{13}C NMR: (75 MHz, $CDCl_3$)

δ 142.5, 128.9, 127.8, 125.7, 103.0, 87.8 (-CH_2**C**≡CSi-), 72.3 (-**C**HOH), 31.0 (-**C**$CHCH_2C$-), 0.06 (-Si(**C**$H_3)_3$) ppm

FTIR: 3396, 3033, 2960, 2902, 2177, 1724, 1604, 1494, 1454 cm^{-1}

EIHRMS: Calcd for $C_{13}H_{18}OSi$: 218.1127, found: 218.1125.

(*R*)-Benzyloxy-6-trimethylsilanyl-hex-5-yn-3-ol (Table A-4, entry 3)



R_f 0.46 (hexane : ethyl acetate 4:1)

Selectivity: 81 % *ee*

Opt. Rot.: $[\alpha]_D^{26}$ = +13 (*c* = 0.05 in $CHCl_3$)

HPLC analysis employing a Daicel Chiracel OD-H column

(Hexane: *i*-propanol 99:1, 0.3 mL/min: t1 = 27.64, t2 = 30.71)

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.30-7.27 (5H, m, -PH-**H**), 4.52 (2H, s, -PhC**H**$_2$O), 3.96 (1H, tq, *J* = 9.03, 3.25 Hz, -C**H**OH), 3.73 (1H, ddd, *J* = 10.18, 7.88, 4.65 Hz, BnOC**H**H-), 3.65 (1H, ddd, *J* = 10.18, 7.65, 4.65 Hz, BnOCH**H**-), 2.46 (1H, dd, *J* = 17.10, 6.05 Hz, -C≡CC**H**H), 2.41 (1H, dd, *J* = 17.10, 6.45 Hz, -C≡CCH**H**), 1.92 (1H, dddd, *J* = 14.32, 6.48, 4.63, 3.25 Hz, $BnOCH_2C$**H**H-), 1.86-1.79 (1H, m, $BnOCH_2CH$**H**-), 0.15 (9H, s, -Si(C**H**$_3)_3$) ppm

^{13}C NMR: (125 MHz, $CDCl_3$)

δ 137.8, 128.4, 127.7, 127.6 (Phenyl), 103.3 (-**C**≡CSi), 87.0 (C≡**C**Si), 73.2 (O**C**H_2) 69.3 (**C**HOH), 68.4 (O**C**H_2), 35.3 (**C**H_2CHOH), 28.5 (**C**H_2C≡C), 0.04 (Si(**C**$H_3)_3$) ppm

FTIR: 3430, 3089, 3065, 3032, 2958, 2926, 2900, 2863, 2175, 1632, 1454 cm^{-1}

EIHRMS: Calcd for $C_{16}H_{24}O_2Si$: 276.1546, found : 276.1506;

List of Publications

1. Silicon-assisted propargylic transfer to aldehydes. **Kiew-Ching Lee**, Man-Jing Lin, Teck-Peng Loh. Chemical Communications (Cambridge, United Kingdom) **2004**, *21*, 2456-2457.

2. Total synthesis of antillatoxin and biological evaluation of antillatoxin and fragments using zebrafish embryo. **Kiew-Ching Lee**, Wayne Wei-Woon Lee, Hong-Yan Song, Teck-Peng Loh. Abstracts of Papers, 229th ACS National Meeting, San Diego, CA, United States, March 13-17, **2005**.

3. Exploration of Diels-Alder reaction with multifunctionalized dienes and dienophiles. Yien-Teng Koo, **Kiew-Ching Lee**, Teck-Peng Loh. Abstracts of Papers, 229th ACS National Meeting, San Diego, CA, United States, March 13-17, **2005**.

4. Natural Occuring Ichthyotoxin causes genetic mutation in Zebrafish embryos: New Bioactive Entity from Synthesis of Antillatoxin and fragments. **Kiew-Ching Lee**, Wayne Wei-Woon Lee, Zhi-Yuan Gong, Yi-Lian Wu, Hong-Yan Song, Teck-Peng Loh. Submitted to Proceeding of the National Academy of Sciences (PNAS).